FEBRUARY 1960
VOL. XXI NO. 2

Circulation

N OFFICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

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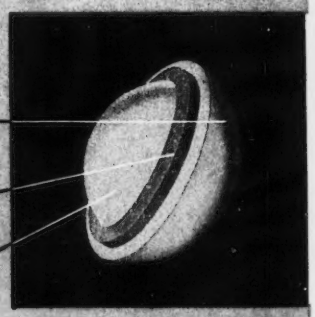

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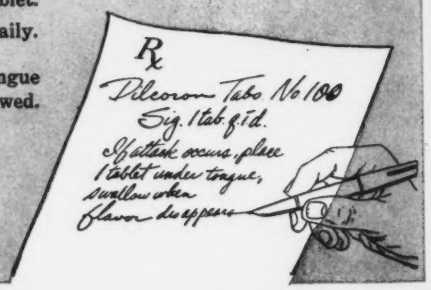

Winthrop LABORATORIES
NEW YORK 18, N. Y.

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AN OFFICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

Editorial

Some Aspects of Pheochromocytoma

THE diagnosis and management of pheochromocytoma still impose problems, although ordinarily the diagnosis is not too difficult. Many of the 66 patients in our series who were later proved to have pheochromocytomas at operation or at necropsy were referred to our associates or us with the diagnosis already made or strongly suspected. On the other hand, we could not verify the previous diagnosis of pheochromocytoma in many cases. Because of the type of operation and the operative risk, the correct preoperative diagnosis is most important.

Pheochromocytomas, tumors of the medullary portion of the adrenal gland, cause paroxysmal or persistent hypertension. In general, patients whose tumors are secreting epinephrine and norepinephrine intermittently have paroxysmal hypertension, and those whose tumors are secreting pressor substances continuously have persistent hypertension.

All patients with paroxysmal hypertension complain of spells or attacks. Excruciating headaches, usually of only 1 to 15 minutes' duration, are the commonest symptom, but frequently they are accompanied by drenching sweats and palpitation. Occasionally paroxysmal sweating and palpitation may occur in a patient without headache but with an unusually high basal metabolic rate. Also present can be tachycardia, nervousness, tremor, dyspnea, great anxiety, pallor or flushing of the face, nausea and vomiting, varying types of distress or pain in the abdomen and chest, pain and numbness in the legs, and tingling and coldness of the hands and feet.

Many of these symptoms are common to a variety of diseases, such as migraine, brain tumor, coronary insufficiency and anxiety tension states with their associated symptoms; therefore, no matter how excellent the story may be for pheochromocytoma and no matter how high the blood pressure is when the attack occurs or how well documented this observation is, the diagnosis must be confirmed by pharmacologic or chemical means before operation is carried out. We had one patient, a physician, who gave an excellent story for paroxysmal hypertension due to pheochromocytoma. He had had repeated spells of severe headache and perspiration associated with marked increase in the blood pressure. Histamine tests, however, repeatedly gave negative results, and the level of pressor amines in the blood before and after stimulation with histamine was always within normal limits. It was subsequently concluded that the patient was having spells of cerebrovascular insufficiency. At this time, almost 2 years later, he is comparatively well, although he has had a coronary occlusion from which he has recovered. Certainly an exploration at the time that he was having his spells would have been extremely hazardous.

Patients with persistent hypertension may have symptoms indistinguishable from those of essential hypertension, but many of them have attacks similar to those experienced by patients with only paroxysmal hypertension.

From the Mayo Clinic and the Mayo Foundation, Rochester, Minn.

The usual picture, however, is that of increasingly severe headaches, excessive perspiration, nervousness, tremor, palpitation, and loss of weight. Most patients are thin, but an occasional patient is obese. The most striking symptom is excessive perspiration, then come nervousness, tremor, and headache.

Laboratory findings from the usual tests are not of much help in the diagnosis of pheochromocytoma causing paroxysmal hypertension. The basal metabolic rate may be high and, if no other cause for hypermetabolism is found, pheochromocytoma should be suspected. The blood sugar may be increased, but values for blood sugar are generally of no help. The excretory urogram may show a mass above one kidney or downward displacement of one kidney, but this only localizes the tumor; it is not diagnostic.

Laboratory findings from the usual tests are of more help in the diagnosis of pheochromocytoma causing persistent hypertension. The basal metabolic rate is frequently very high, often +40 to +60 per cent and in 1 case +140 per cent; hyperthyroidism and other causes of hypermetabolism must be excluded in these cases. The blood sugar is frequently high, but is not diagnostic. The excretory urogram has the same value as it does in pheochromocytoma causing paroxysmal hypertension.

Two drugs are now used almost exclusively by us in testing for pheochromocytoma.[1] Histamine is used when pheochromocytoma causing paroxysmal hypertension is suspected. The results are not always accurate, but in our experience histamine gives a more accurate test than tetraethylammonium chloride. A dose of 0.05 mg. of histamine base in 0.5 ml. of isotonic solution of sodium chloride is injected rapidly intravenously. The result is considered positive when, after an initial decrease 30 seconds after the injection, the blood pressure rises significantly, with a maximum, at the end of 2 minutes, considerably above the maximum reached during the cold pressor test. We have emphasized on previous occasions and we emphasize again the extreme importance of determinations of basal blood pressure and the cold pressor test in interpreting the results of the histamine test.[2] The cold pressor test is as much a part of the histamine test as is the injection of the histamine itself. If the rise in blood pressure 1 to 2 minutes after the injection of histamine is significantly greater than the maximal rise in blood pressure after the cold pressor test, then the pharmacologic test may be considered as positive for pheochromocytoma. Failure to compare the increase after histamine with the increase during the cold pressor test is the cause of many incorrect interpretations of the histamine test. The rise in blood pressure after the cold pressor test must be evaluated as well.

Phentolamine hydrochloride (Regitine) is used for tests on the patient with sustained hypertension suspected of having pheochromocytoma. Piperoxan is no longer used, mainly because it causes more unpleasant side reactions than phentolamine. Results are considered positive if the blood pressure decreases more than 35 mm. of mercury systolic and 25 diastolic from the based level and remains decreased for 3 to 4 minutes. A slight decrease in the blood pressure in the first 2 minutes after intravenous injection with a return to basal level is not a positive result. Five milligrams of phentolamine (Regitine) are injected rapidly for this test.

Basal blood pressures should always be determined before a pharmacologic test is made on a patient suspected of having pheochromocytoma. Drugs such as narcotics, sedatives, and cyanates should be withheld for at least 4 hours before tests, as they may produce false-positive results. Antihypertensive drugs will produce false-negative results and hydralazine (Apresoline), at least, should be withheld for 8 to 10 days before these tests.

When the basal blood pressure is less than 170 mm. of mercury systolic and 110 mm. diastolic, histamine is the drug of choice for testing, but when the blood pressure is more than 170/110, phentolamine is the drug of choice. When the blood pressure rises greatly after the injection of histamine, phentolamine is employed to lower it. Thus both histamine

and phentolamine may be used for the same patient having a pheochromocytoma, and positive results from the 2 tests for the tumor may be obtained.

The diagnosis must be made with the aid of pharmacologic and chemical tests. In evaluating the results of these tests, it is well to remember that all the tests can give falsely positive and falsely negative results, and that only by careful appraisal of all the symptoms, findings, and laboratory data available can a decision be reached that exploration is necessary.

The pharmacologic tests with histamine and phentolamine can be performed by any physician, providing the necessary precautions are exercised. If the results of the tests are doubtful or negative, the test should be repeated. No single test is always completely reliable. If doubt still exists, measurement of the catecholamines in the urine and the pressor amines in the blood should be made. These tests may necessitate reference of the patient to a medical center where facilities for such studies are available.

Chemical quantitation of the pressor amines (epinephrine and norepinephrine) in the blood is the most direct method of establishing the presence of a functioning pheochromocytoma. However, a pheochromocytoma must be secreting epinephrine or norepinephrine spontaneously, or the sample of blood for analysis should be collected at the height of the blood pressure response to histamine. Otherwise the finding of a normal concentration of pressor amines in a sample does not exclude pheochromocytoma.

The concentration of pressor amines in the blood is nearly always less than 3.5 μg. per liter of plasma in cases of essential hypertension and does not increase significantly after stimulation with histamine in such patients. We have found increased concentrations in the blood in some patients taking tetracycline (Aureomycin) and also in patients with renal insufficiency, jaundice, increased intracranial pressure, or lymphoma. Thus it is important to realize that other conditions may cause elevated concentrations of pressor amines in the plasma that may lead to a false diagnosis of pheochromocytoma. Hemolysis or hyperbilirubinemia or both can interfere with the chemical analysis and cause erroneously elevated concentrations in the blood. Only under conditions in which the tumor is actively secreting will the results be positive. Finally, it is important to remember that elevated concentrations of pressor amines in the blood may result from the use of some epinephrine-like substances. We have observed this in 8 patients who were using epinephrine by nebulizer. Even the use of vasoconstrictor agents for nasal stuffiness is under suspicion as a cause of elevated levels of pressor amines in the blood.

The qualitative test for urinary catecholamines in 24-hour specimens of urine provides another useful procedure for the detection of a pheochromocytoma that is releasing catecholamines. When the result is positive, quantitative determination of the catecholamines in hydrolyzed urine provides additional information in establishing the diagnosis. Values of more than 250 μg. per 24-hour specimen of urine are considered positive for pheochromocytoma. The results of the test are positive only under conditions in which the tumor is actively secreting the pressor substances. Salicylates will produce falsely positive results.

In patients suspected of having a pheochromocytoma that is causing paroxysmal hypertension, it is our practice to perform a histamine test and in some cases to determine the amount of pressor amines in the blood before and after the injection of histamine. If the patient has the tumor, the result of the histamine test is usually positive.

In patients suspected of having a pheochromocytoma that is causing persistent hypertension, it is our practice to do a phentolamine test or to test a 24-hour specimen of urine for catecholamines. If the result is positive, the diagnosis may be established by finding elevated values for pressor amines in the blood.

Once the diagnosis of pheochromocytoma has been made, localization of the tumor is not necessary. Perirenal insufflations of air are unnecessary and hazardous. We recently had a patient, a girl aged 16 years, who went into shock after perirenal insufflation of air elsewhere. Exploration subsequently revealed a pheochromocytoma of the right adrenal gland.

Exploration usually is carried out through a transverse upper abdominal incision.[2, 3] This type of exposure allows the surgeon to explore both adrenal regions and the abdomen. Tumors have been found beneath the hilus of the liver, around the kidneys, and along the great vessels of the abdomen.

These tumors are usually single and benign and usually occur in one adrenal gland. However, they may be multiple on one side, on both sides, or may be located wherever chromaffin tissue is found. They may be benign but subsequently become malignant and metastasize.

Careful study of 66 patients with pheochromocytoma has suggested that tests should be undertaken on the following types of patients: (1) any patient who complains of spells associated with severe headache and perspiration, with or without other symptoms; (2) any patient with hypertension who is young, or has a short history of hypertension or severe hypertension of groups 2 to 4, or is thin and has a history of fluctuating hypertension; (3) any patient with hypermetabolism without hyperthyroidism; (4) any patient who responds in a paradoxical manner to the ganglionic blocking agents; and (5) any patient who responds unsatisfactorily to an anesthetic and whose blood pressure rises. For the last-mentioned patient, administration of anesthetic should be stopped immediately.

If these criteria are followed, it is unlikely that a pheochromocytoma will be missed. The greatest obstacle to correct diagnosis is previous medication before all tests. It is true that many patients will undergo tests and that many tests will be performed without yield, but to suspect a pheochromocytoma, confirm its presence, and then have it removed successfully may be lifesaving. Unfortunately, not all patients are cured when the tumor is removed. A few of the tumors are malignant, and some that were first considered benign have become malignant and metastasized.

WALTER F. KVALE
GRACE M. ROTH

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Editorial

The Heart Association and the Physician

DIRECT publication by the American Heart Association of its own scientific journals, beginning with the January issue of *Circulation,* marked an important milestone in the Association's more than 35-year history. During those years and especially during the past decade in which the Association has functioned as a voluntary health agency, its relationship to the medical profession has been one of mutual benefit and service.

The title of this editorial gives me the discretion of two approaches: What does the physician get from the AHA? What does the physician give to the AHA?

I had best start with the second of these questions, as without contributions in terms of time, and physical and mental effort, and financial sacrifice from many physicians, there would be no Heart Association. Over the past 35 years, leadership of the American Heart Association by a series of presidents, all of them outstanding physicians of high scientific caliber, has given the Association prestige and ever increasing influence in the whole field of medicine. It has only resulted, however, from a vast and selfless investment of time and energy by these men. This willingness to work has been duplicated many thousands of times all over the United States by general practitioners, internists, surgeons, pediatricians, pathologists, medical investigators, and many others who as officers and committee members of the American Heart Association and its Affiliates and Chapters have repeatedly and effectively devoted their talents without compensation to seeing that the professional guidance of Heart Association activities was constantly maintained at the highest possible level. I wonder if it is known, for example, that each member of the Research Committee of the American Heart Association devotes more than one month each year to the work of reviewing and considering applications. Or that at a single committee meeting which I attended in New York in September, there were eminent physicians who—leaving office, lecture room, and laboratory—had come from California, the state of Washington, Ohio, Georgia, North Carolina, Massachusetts, and Iowa just to contribute to a single day of discussion.

Finally, but not least, there is the core of medical strength in the group of physicians forming the fine medical staff of the Association, the medical director and his associates, who as full-time employees, direct the day-to-day work involving medical content. This in brief is what physicians put into the Association: long hours of person-to-person discussion, committee work, review of documents, writing of policy, speaking, and travel; this plus contributions in actual dollars from the great majority of the total medical profession.

What does the physician get out of the American Heart Association? He gets membership in the outstanding voluntary health agency in the field of cardiovascular disease. There are now 55 Affiliates in every state, the District of Columbia, and Puerto Rico, plus some 296 Chapters within their jurisdiction. The American Heart Association is built upon a firm democratic foundation with an appropriate balance maintained between its medical and nonmedical membership. The latter is predominantly responsible for raising the funds without which the pursuit and application of new knowledge are impossible, and for business management and public relations. Except for matters requiring specialized professional skills however, no sharp line divides the functions and responsibilities of the two groups. The physician members frequently give valuable assistance in nonmedical areas and are playing an increasing role in the fund-raising campaigns. The total membership of the American Heart Association and its Affiliates numbers close to 36,000, of which 20,500 are physicians, medical scientists, and members of other health professions. Physicians and medical scientists are members of all the principal committees such as those on budget, finance, policy, and fund raising, and are usually

chairmen of those committees most concerned with medical and scientific programming.

If the physician is a practitioner, he gets the benefit of many types of educational activities. The monthly journal which you are reading is one of these, as is *Modern Concepts of Cardiovascular Disease* distributed each month to 102,000 physicians. He may receive also *The Heart Bulletin* co-sponsored by the American Heart Association, the American Academy of General Practice, and the National Heart Institute. He has an opportunity to attend the annual scientific sessions of the Association and to attend local scientific meetings at home or near home sponsored by most local Heart Association Chapters and Affiliates. Furthermore, for his patients, there are useful informative booklets and pamphlets on many subjects including rheumatic fever, rheumatic fever prevention, low-sodium diets, congenital heart disease, and so forth. These are particularly aimed for patient education and to save him time in his practice.

The community-service programs of the Heart Association provide another tool of tremendous value to the physician. They assist in developing, coordinating, and improving the local facilities and services that will aid him in the total care of his patients. A typical community-service program of the Heart Association might include rehabilitation services, a work-evaluation unit, clinics for heart patients, rheumatic fever prevention and school health programs, work simplification for the cardiac housewife, vocational counselling, nutritional guidance for heart patients, and home-care services. Heart Association policies as well as budget preclude direct payment for medical care and drugs. Instead, Association efforts are focused on those activities that will bring the greatest benefit to the greatest number of people.

If the physician is an investigator, he can particularly profit from the scientific articles in *Circulation Research* published by the Association as well as from the other activities on various phases of research appearing in *Circulation*. *Circulation Research* was created particularly to offer investigators a chance to publish their own work within a reasonably short time, thus reducing the gap that so often exists in the publication of scientific material. The investigator's research itself can be supported by fellowships and grants from the American Heart Association and its Affiliates and Chapters, providing it receives the approval of the appropriate research committee. Last year, $1,562,748 was paid by the American Heart Association for 233 grants-in-aid. To 181 other investigators went checks last year for a total of $1,450,651 covering several categories of direct support, categories which ranged from career investigators down to junior fellowships. The annual scientific sessions as well as smaller meetings on special scientific topics are available to permit exchange of ideas and presentation of results.

There is another type of benefit derived from the existence of the American Heart Association and that is the satisfaction obtained by those physicians who work for it. This may sound like a platitude to those unused to the atmosphere of a voluntary health association. It is not a platitude to those physicians who have placed their shoulders to the wheel. The satisfaction of seeing research, community service, and education programs grow and of investing wisely the money entrusted to the Association by the public are very real. The ever growing strength of this bulwark of a free society, achieved by service and by selflessness, gives to every physician especial support for the freedom of his or her profession.

Lastly, to each physician as to every citizen, there is on the one hand the threat of sudden death or disability from cardiovascular disease, and on the other the vision that through research supported by the Association and later applied at the community and patient level, such a catastrophic snuffing out of life will be prevented in the future.

OGLESBY PAUL, M.D.
President-Elect,
American Heart Association

Familial Muscular Subaortic Stenosis

An Unrecognized Form of "Idiopathic Heart Disease," with Clinical and Autopsy Observations

By Lawrence B. Brent, M.D., Akio Aburano, M.D., Don L. Fisher, M.D., Thomas J. Moran, M.D., Jack D. Myers, M.D., and W. Jape Taylor, M.D.

SUBAORTIC stenosis has been regarded as a rare condition, usually caused by an easily demonstrable fibrous ridge attached to the left ventricular myocardium below the aortic valve. Our recent experience, however, suggests another form of subvalvular stenosis that is caused by muscular hypertrophy, occurs with multiple cases in an affected family, requires special attention in differential diagnosis, and is not operable.

Recently, variant types of aortic stenosis have been encountered in the laboratory and at the operating table.[1-5] Preoperative tests may show a significant systolic pressure gradient between the left ventricular outflow tract and the aorta, which is considered an indication for surgical relief of the obstruction, whether valvular or subvalvular in location. Subsequent operation occasionally reveals an atypical obstruction[6, 7] apparently caused by muscular hypertrophy, which cannot be repaired.

Our interest in subaortic stenosis was aroused by a patient in whom a clinical diagnosis of aortic stenosis was made, but at operation no aortic or subaortic stenosis could be demonstrated. The patient died postoperatively of acute tubular necrosis, and at autopsy a "functional" muscular obstruction of the left ventricular outflow tract was found.

Because of a strong history of heart disease and sudden death in the patient's family, a survey was made of the remaining members. Several months later an uncle of the patient who had been examined in the survey dropped dead in his home, and at autopsy the findings in the heart were identical. Then a third patient was studied, unrelated to the first 2, but with similar clinical findings and a strong family history of heart disease. About 6 weeks later this patient also died suddenly at home. Autopsy revealed the same cardiac changes. The clinical and autopsy observations are presented in this report, along with the family pedigrees suggesting familial heart disease with Mendelian dominant inheritance.

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Supported by grants from The Western Pennsylvania Heart Association and The Life Insurance Medical Research Fund.

Case Reports

Family A

Patient 1A

A 29-year-old white man was first seen at age 18 years by his local physician in 1947, after being rejected from military service because of a heart murmur. He had no complaints at that time and there was no past history of rheumatic fever or of other heart disease. Examination showed slight cardiac enlargement, an aortic systolic murmur, and a blood pressure of 124/60. In 1957, 10 years later, he was hospitalized because of palpitation and a rapid heart rate of 4 years' duration. The blood pressure then was 140/70. There was slight cardiomegaly and a grade-III systolic murmur at the apex and along the left sternal border. The chest roentgenogram showed left ventricular enlargement, and the electrocardiogram demonstrated high voltage over the left chest leads. He was treated with digitalis and quinidine with some relief of the palpitation.

He was admitted to the Presbyterian Hospital Unit of the University of Pittsburgh Medical Center at the age of 29, complaining again of palpitation and dyspnea on effort for 4½ years. There were 3 or 4 syncopal attacks in the 2 years preceding admission. He was constantly fatigued and noted swelling of his ankles on occasion. The family history revealed one brother who had died suddenly at age 29 (patient 3A) of "rheumatic"

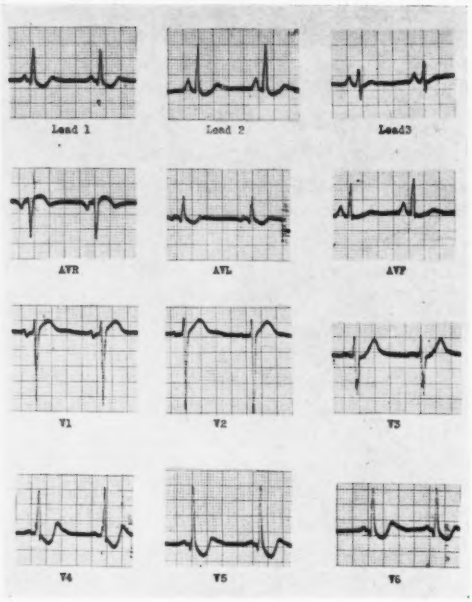

Figure 1
Electrocardiogram of patient 1A.

heart disease, a nephew, (patient 4A) who had surgical exploration in another hospital for pulmonic stenosis, and his father who died of heart disease in 1953.

The blood pressure was 150/70, and the heart rate was regular at 96 per minute. There were no signs of congestive heart failure and no cyanosis. A vigorous apical pulsation was palpable in the fifth and sixth left intercostal spaces, 2 cm. to the left of the midclavicular line, and a systolic thrill was felt at the apex and lower left sternal border. A harsh, musical, grade-IV systolic murmur was heard loudest at the apex and along the lower left sternal border, but transmitted clearly to the neck, axillae, and posteriorly. The aortic and pulmonic second sounds were of normal intensity. There was an apical presystolic and protodiastolic gallop not affected by deep inspiration. The peripheral arterial pulses were all of equal intensity and appeared widened in amplitude with a definite pulsus bisferiens.

The laboratory data, including urinalysis, hemogram, blood sugar, blood urea nitrogen, electrolytes, proteins, and prothrombin concentration were normal. The serum cholesterol was 290 mg. per cent and the protein-bound iodine was 4.4 gamma per cent. The antistreptolysin O titer was normal and C-reactive protein was negative. The electrocardiogram demonstrated left ventricular

Table 1
Right and Left Heart Catheterization

Position	Family A Patient 1 Pressures mm. Hg Systolic/Diastolic (mean)	Family B Patient 1
Left atrium	(12)	(14)
Left ventricle	226/12	134/12-14
Aorta, arch	131/71 (90)	84/52 (66)
Right atrium	(1)	(4)
Right ventricle	32/1	24/4-6
Pulmonary artery	26/5 (13)	24/13 (17)
Surface area $M.^2$	1.6	1.5
O_2 consumption ml./min.	225	221
Cardiac index L./min./$M.^2$	2.3	3.16
Aortic valve area $cm.^2$	0.5	0.8

preponderance (fig. 1) and the chest x-ray film (fig. 2) showed a normal-sized heart with a contour suggesting left ventricular enlargement. On fluoroscopy, the left ventricle alone appeared enlarged. The aortic and pulmonary artery pulsations were normal. There was no poststenotic dilatation of the aorta and no calcification of the aortic valve. A combined heart catheterization was performed, including a standard right heart catheterization and percutaneous left atrial puncture (table 1). Simultaneous left ventricular and left brachial artery tracings demonstrated "severe aortic stenosis" with a calculated valve orifice[8] of 0.5 $cm.^2$ (fig. 3).

On May 5, 1958, the patient underwent open-heart surgery with total cardiac bypass and cardiac arrest with potassium citrate. The ascending aorta was opened with a longitudinal incision and the aortic valve was found to be perfectly normal. The surgeon passed his finger down into the outflow tract of the left ventricle and found no evidence of subvalvular stenosis. Exploration of the right ventricle revealed a markedly hypertrophied ventricular septum and a small right ventricular chamber. After restoration of cardiac activity, direct recordings again demonstrated a systolic pressure gradient between the left ventricular outflow tract and the aorta. The immediate postoperative course was complicated by high fever, blood loss, hypotension, and finally acute renal damage, resulting from sustained hypotension or from incompatible blood. He died 8 days postoperatively of uremia.

Autopsy Findings. The principal anatomic findings were subaortic stenosis of a muscular hypertrophy type and acute tubular necrosis. Other

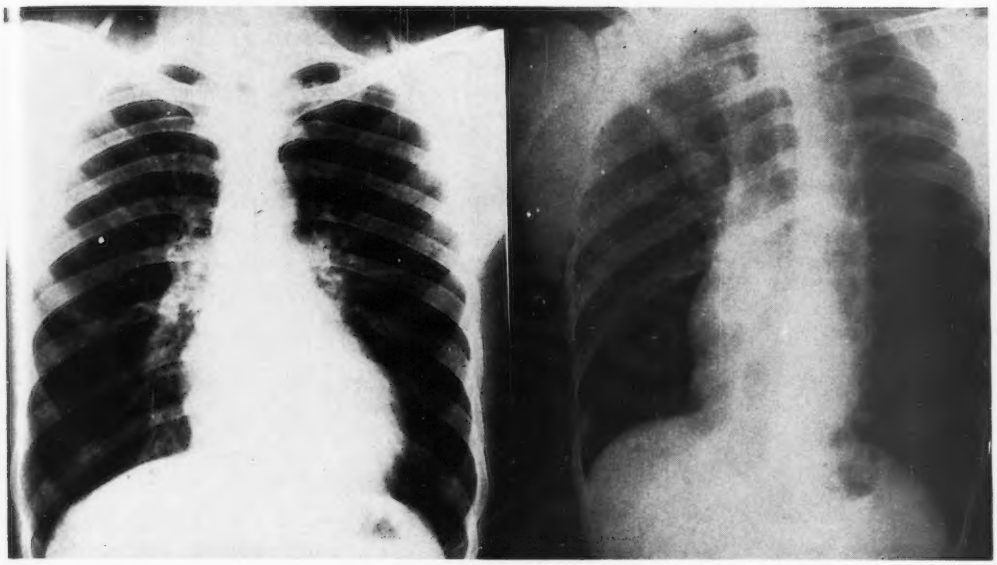

Figure 2

Posteroanterior and left anterior oblique roentgenograms of patient 1A.

pertinent findings were bronchopneumonia, a postoperative hematoma of the anterior mediastinum, bilateral hemothorax, and infarcts of the spleen and right kidney.

The heart was globular and large, weighing 560 Gm. The aortic valve was normal. A finger was easily inserted through the valve but approximately 2.5 cm. from the valve it met some resistance, but not complete obstruction, from a prominent muscle mass in the area of the interventricular septum. A similar muscle mass was felt protruding into the outflow tract of the right ventricle, again in the area of the septum. When the heart was opened, striking hypertrophy of the myocardium of the entire left ventricle was demonstrated. The septal muscle bulged into the left and right ventricles (figs. 4 and 5). The hypertrophy was especially prominent on the left side of the heart, and as the heart was closed and viewed from above, the obstruction of the left ventricular cavity could be seen at a level 2.5 cm. below the base of the aortic valve. Below this level the cavity of the left ventricle was greatly narrowed. Above the obstruction the outflow tract was dilated to form a small chamber, extending up to the valve. The endocardium over the upper portion of the hypertrophied muscle mass was thick, opaque, and gray-white, but it did not form a fibrous ridge or shelf and did not contribute to the obstruction of the outflow tract. The aortic and mitral valves were normal, except that the aortic valve was small, measuring 5.0 cm. in circumference. The mitral valve measured 7.5 cm. in circumference. The left ventricular wall measured 2.3 cm. in average thickness and the interventricular septum measured 3 cm. in thickness. The tricuspid and pulmonic valves appeared normal. The tricuspid valve measured 10.5 cm. in circumference, the pulmonic 5.5 cm. There was slight patchy thickening of the endocardium of the right ventricle. The coronary arteries were patent and smooth throughout.

Microscopic examination of the heart (fig. 6) showed moderate enlargement of the individual fibers. In a few areas the muscle fibers had a bright pink, smudged appearance which was regarded as a terminal change, probably related to the ischemia at operation. There were patchy areas of interstitial fibrosis and occasional small areas of replacement fibrosis. Sections of the left ventricle in the subaortic region showed irregular thickening and increased fibrous tissue in the endocardium and the underlying myocardium (fig. 7). The fibrosis did not extend deeply into the myocardium and there were no vascular changes in this region. Masson's trichrome stains showed an increase in collagen. No increase in elastic fibers was demonstrated by Verhoeff elastic tissue stains.

Patient 2A

Patient 2A was the 54-year-old paternal uncle of patient 1A. He was examined in August 1958 during a survey of the family. He had noted

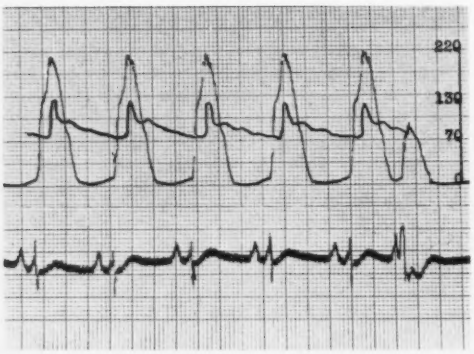

Figure 3

Superimposed, simultaneous pressure tracings obtained in the left ventricle and left brachial artery in patient 1A.

dyspnea on exertion and frequent palpitation of several years' duration. Several months previously he had also experienced a syncopal attack while at work as a lumberjack. He denied orthopnea, chest pain, paroxysmal nocturnal dyspnea, and edema. He had never been told he had high blood pressure. During hospitalization for operative repair of a perforated peptic ulcer in 1951 no cardiovascular complaints were elicited. Physical examination then demonstrated no cardiac enlargement, the blood pressure was 134/76, and there was a systolic murmur at the apex. In August 1958, the blood pressure was 130/80 and the heart was regular at 84 per minute. There were no signs of congestion nor cyanosis. The heart was enlarged 2 cm. beyond the midclavicular line in the sixth left intercostal space. There was a vigorous apical thrust and a harsh, grade-III systolic murmur was heard over the precordium, loudest at the apex and along the lower left sternal border, well transmitted to the aortic area and neck. The aortic and pulmonic second sounds were of equal intensity. The pulses were thought to be normal to palpation. The electrocardiogram demonstrated high voltage over the left precordial leads, but no evidence of strain. Hospitalization was advised for special diagnostic tests, but was refused. His condition did not change until December 24, 1958, when he suddenly dropped dead.

Autopsy Findings. No arterial or venous anomalies were found. Externally the heart exactly resembled that of patient 1A. It also weighed 560 Gm. When the finger was inserted through the aortic valve, the valve appeared normal but considerable resistance was encountered in the outflow tract approximately 1.5 cm. below the valve. The finger was pushed through this narrowed area with considerable difficulty, although no fibrous bands or valves were encountered. The resistance was obviously caused entirely by muscular hypertrophy of the ventricular wall. A prominent muscle mass was encountered below the pulmonic valve but there was no obstruction.

When the heart was opened, the upper portion of the muscle mass and the obstruction were encountered 1.5 cm. from the base of the aortic valve (fig. 8). The outflow tract was somewhat dilated above this level and below it the cavity was almost completely obliterated. The myocardium of the left ventricle averaged 2.0 cm. in thickness, and the interventricular septum measured 2.5 cm. in thickness. The valve circumferences were as follows: tricuspid 12 cm., pulmonic 7 cm., mitral 10 cm., and aortic 6.5 cm. The coronary arteries contained a few small atheromata but there was no stenosis. The other findings were similar to the first case. Microscopic examination showed only slight endocardial thickening with no involvement of the myocardium. Again the individual muscle fibers were hypertrophied. There were no vascular changes.

Patient 3A

Patient 3A was a brother of patient 1A. His local physician first saw him in 1936 at age 16 years because of pneumonia. A systolic murmur was noted then but there were no cardiovascular symptoms. In November 1947 he was hospitalized with infectious hepatitis. He had shortness of breath on exertion and a nonproductive cough, but orthopnea, paroxysmal nocturnal dyspnea, and edema were not mentioned. His past history had revealed rejection from the military service because of a heart murmur. Examination gave no evidence of cardiac enlargement and no murmurs were described. The blood pressure was 140/80. Chest x-ray was reported to show a prominent left ventricle. A diagnosis of rheumatic heart disease was considered even though there was no antecedent rheumatic history, cardiomegaly, or murmur. He was rehospitalized in November 1948 with a gunshot wound of the left arm and subsequent amputation. Examination revealed the blood pressure to be 120/64. No cardiomegaly or murmurs were described at that time and there was no report of a chest x-ray or electrocardiogram. Several months later, 2 or 3 syncopal attacks occurred, and the patient dropped dead on the street. No autopsy was performed.

Patient 4A

Patient 4A, a 12-year-old boy, is the son of patient 3A. At the age of 9 months, he was admitted to a hospital with dyspnea and fever. Physical findings were compatible with bilateral bronchopneumonia. No cardiomegaly or heart murmur was

Figure 4

Photograph of the left side of the heart from patient 1A showing location of the subaortic stenosis (arrow).

Figure 5

Photograph of the right side of the heart from patient 1A showing the prominent muscle mass in the right outflow tract.

described. The x-ray revealed bilateral bronchopneumonia and a normal heart size. Two years later, in 1948, he was admitted for treatment of cervical adenitis. Again, no cardiac enlargement or murmur was noted. In 1951 the patient was seen by the local physician with complaints of frequent respiratory infections and physical underdevelopment. At this time the blood pressure was 108/70, a systolic murmur was heard at the apex, and the electrocardiogram revealed right ventricular preponderance. The physician considered the diagnosis of an interventricular septal defect. In 1954, at the age of 8 years, the patient was rehospitalized with acute bronchitis. Examination revealed slight cardiomegaly and a grade-III, harsh, systolic murmur along the lower left sternal border and apex. X-ray films revealed ventricular enlargement. Again, the diagnosis of interventricular septal defect was made. In 1956 surgery was performed at another hospital for pulmonic stenosis, but it was not found. He has been followed since at Children's Hospital at this Medical Center, where the chief complaint has been intolerance of exercise. Examination revealed cardiomegaly, a systolic thrill, and a grade-III to IV systolic murmur along the left sternal border that was poorly transmitted to the neck. Chest x-rays and the electrocardiogram suggested biventricular enlargement. A right heart catheterization was performed in June 1958 with normal findings.

Patient 5A

Patient 5A, a 10-year-old boy, a nephew of patient 1A, is asymptomatic. Examination during a survey of the family in August 1958 revealed the apex impulse to be 1 to 2 cm. beyond the left midclavicular line with a forceful apical thrust. There was a grade-III systolic murmur loudest at the apex and lower left sternal border transmitted to the aortic area and neck. Pulses were thought to be normal. The electrocardiogram was normal. The chest x-rays and fluoroscopy were suggestive of left ventricular enlargement. The brachial artery pulse tracing was normal.

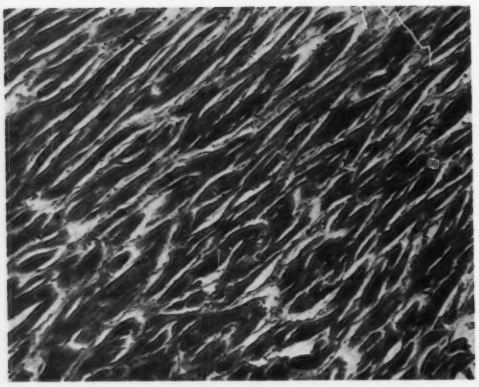

Figure 6

Photomicrograph of heart from patient 1A showing hypertrophy of individual fibers and moderate interstitial edema. Hematoxylin and eosin × 140.

Patient 6A

Patient 6A is a 24-year-old brother of patients 1A and 3A. He is asymptomatic. Examination did not reveal cardiomegaly. There was a grade-II systolic murmur at the apex and lower left sternal border. There were no congestive signs or cyanosis. Arterial pulses were all normal. The electrocardiogram was normal.

In addition to these 6 patients, patient 7A, a paternal uncle of patient 1A, suddenly dropped dead while standing at work 25 years ago. He was approximately 25 years old at the time and was not known to have had any cardiovascular symptoms. An autopsy was not performed. Patient 8A, a first cousin of patient 1A, was admitted to another hospital in July 1946 with the diagnosis of rheumatic heart disease, acute congestive heart failure, and lobar pneumonia. He died 48 hours after admission. There was no well-substantiated antecedent rheumatic history. No autopsy was performed. His father, patient 9A, had been admitted to another hospital in 1945 complaining of palpitation, tachycardia, and ankle edema. He was found to have cardiomegaly, an apical systolic murmur, and enlargement of both liver and spleen. He was thought to have had rheumatic heart disease and subacute bacterial endocarditis. He subsequently died of this illness.

The father of patient 1A died at age 58 years of coronary artery disease, which is well documented by hospital records, but no autopsy was performed. The mother is 60 years of age and living without cardiac complaint. Her physical examination and electrocardiogram were negative. The paternal grandfather died at age of 60 years of pneumonia. Of the 2 surviving uncles, one is living and well at the age of 62 years and the other is suffering from coronary artery disease and congestive heart failure at the age of 70 years. Another uncle died quite suddenly at the age of 54 years, but no information is available regarding the nature of his death.

Family B

Patient 1B

Patient 1B was a 34-year-old white housewife, admitted to Allegheny General Hospital December 29, 1958, with a chief complaint of syncope and chest pain. She had been well until January 1949, when an apical systolic heart murmur was heard during hospitalization elsewhere for an ectopic pregnancy. The blood pressure was then 94/64. Routine laboratory work was negative and the chest x-ray was described as normal. She had no cardiovascular complaints at that time. She remained well until July 1954, when she had a syncopal attack followed by chest pain, which required rehospitalization. Her only other complaint was dyspnea on exertion. Examination revealed an enlarged heart, 1 to 2 cm. outside the left midclavicular line in the sixth intercostal space and a grade-III systolic murmur at the apex and along the lower left sternal border. Routine laboratory data were not remarkable. The chest x-ray is reported as suggestive of "mitral heart disease." An electrocardiogram demonstrated deep S waves over the right precordial leads but little else to suggest left ventricular hypertrophy. She was treated with digitalis without relief. In October 1956, and again in January 1957, she fainted, each time awakening with chest pain. Since she was 8½ months' pregnant on the latter occasion, she was rehospitalized. Examination of the cardiovascular system revealed a grade-III apical systolic murmur and a blood pressure of 100/60. The routine laboratory data were negative. She was treated with digitalis and bed rest and had a successful delivery.

She was first seen at Allegheny General Hospital in December 1958. On the day of admission, she had been playing with her 2-year-old son, when she suddenly fainted. On awakening, she noted pain in the precordial area radiating to her right arm, which gradually subsided. She also complained of shortness of breath with moderate exertion, and fatigability.

Her father had died of alcoholism and heart disease at the age of 47 years. Her mother, age 58 years, was living and well. Her brother had died at age 14 years, supposedly of an enlarged thymus, but no autopsy was performed. One sister had had rheumatic fever and 4 sisters were living and well. At the time of her admission to Allegheny General Hospital, her daughter was also in the hospital

with a diagnosis of rheumatic myocarditis. One son, aged 7 years, reportedly had a clinical diagnosis of interventricular septal defect.

The patient's blood pressure was 92/58, heart rate 86 and regular, and respirations 20. Arterial pulses were all of equal intensity. The heart was enlarged 2 cm. beyond the left midclavicular line in the sixth intercostal space. There was a grade-III systolic murmur loudest at the apex and along the lower left sternal border, transmitted to the neck. The aortic and pulmonic second sounds were of equal intensity. The electrocardiogram demonstrated left ventricular preponderance (fig. 9), and the chest x-rays and fluoroscopy were suggestive of left ventricular enlargement (fig. 10). Combined left and right heart catheterization via percutaneous left and right atrial puncture demonstrated a 50-mm. systolic gradient across the left ventricular outflow tract (fig. 11) with a calculated aortic valve area[8] of 0.8 cm.^{2} (table 1). Despite repeated attempts, the catheter did not pass from the left ventricle to the aorta. In view of the severity of the patient's clinical course and the catheterization findings, an operation was tentatively planned approximately 6 weeks after the catheterization. Because of the family history and our previous experience with family A, however, further diagnostic tests were also planned, including cinecardioangiography, in an attempt to localize the obstruction. Approximately 1 month after discharge the patient suddenly dropped dead at home.

Autopsy Findings. There were no anomalies of the arteries or veins and there were no emboli in the pulmonary arteries. The heart weighed 420 Gm. and was globular, with prominence of the left ventricle. As in the 2 previous cases, the left ventricular cavity was almost obliterated by the greatly hypertrophied muscle mass extending into the outflow tract, and as in the second case, considerable resistance was encountered when the finger was forced into the left ventricle. The obstruction to the outflow tract occurred 1.0 cm. below the base of the aortic valve. The left ventricular wall measured 2.2 cm. in thickness. A prominent muscle mass extended into the right ventricle but without obstruction of the outflow tract. The valves were entirely normal. There was minimal atheromatous involvement of the intimal surface of the coronary arteries, but there was no stenosis or obstruction. In all other respects this heart resembled the 2 previously described. Microscopic examination showed only slight endocardial thickening over the subaortic region and moderate hypertrophy of the individual muscle fibers.

Patient 2B

Patient 2B is the 11-year-old daughter of patient 1B. She was admitted to Allegheny General Hospital in December 1958 complaining of a severe sore throat. Several days prior to admission she had noted soreness of her throat and headache, and was found to have a temperature of 104 F. She also complained of aches in her leg and pain in the right elbow but denied swelling of any joint.

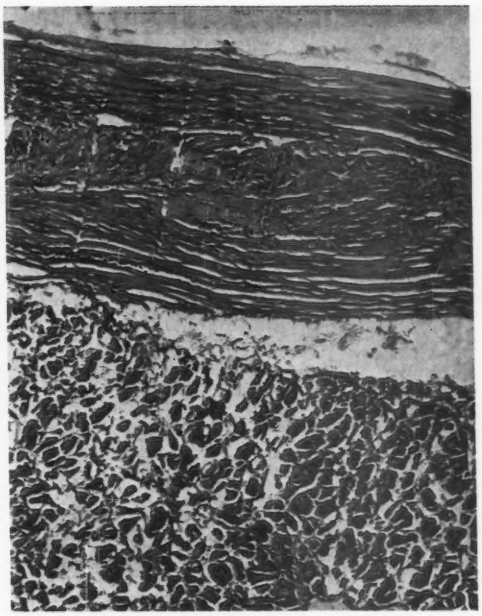

Figure 7

Photomicrograph of heart from patient 1A showing area of subendocardial fibrosis. Hematoxylin and eosin × 140.

The past history, including the neonatal period, was not remarkable except for the usual childhood diseases. One year prior to admission a complete physical examination was said to have been normal.

The heart rate was 80 and regular and the respirations were 20. The physical findings revealed enlarged and inflamed tonsils, but no exudate was seen. The pharynx was injected and there was moderate anterior cervical adenopathy. The lungs were clear to percussion and auscultation. The heart was not enlarged, but there was a grade-III systolic murmur located at the apex and lower left sternal border. The aortic and pulmonic second sounds were normal and the arterial pulses were equal in the arms and legs. The routine laboratory examinations were normal. Numerous determinations of C-reactive protein were negative and the antistreptolysin O titer ranged between 50 and 125

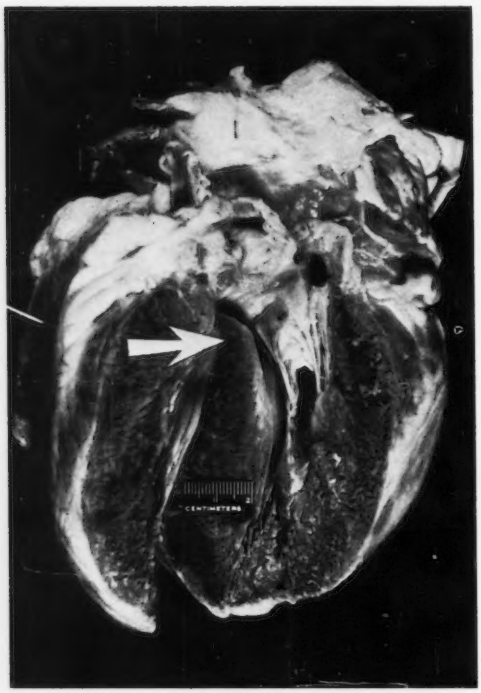

Figure 8

Photograph of heart from patient 2A showing a cut through the interventricular septum and the point of subaortic stenosis (arrow).

Todd units. Several nose and throat cultures did not reveal beta hemolytic streptococci. The chest x-ray films and fluoroscopy demonstrated slight widening of the heart, probably due to left ventricular enlargement. There was no poststenotic dilatation of the aorta. The electrocardiogram, on admission, was not remarkable except for large P waves suggesting atrial enlargement. Subsequently left ventricular hypertrophy developed progressively during a 1-month period. The child was treated with complete bed rest, large doses of adrenal cortical steroids, and salt restriction. There was, however, no improvement either clinically or electrocardiographically. Right heart catheterization was normal with the exception of a pulmonary capillary wedge pressure of 21 mm. Hg. The contour of the wedge tracing does not suggest mitral insufficiency. A left heart catheterization was proposed but the patient's father refused permission. At present, she is at a local rehabilitation center.

Patient 3B

Patient 3B was a brother of patient 1B. In August 1941 he was 14 years of age and in apparently good health when he suddenly dropped dead while skipping rope in his backyard. No autopsy was performed and the cause of death was undetermined.

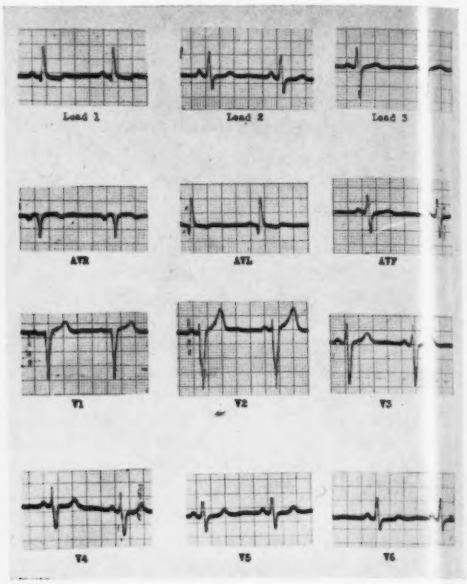

Figure 9

Electrocardiogram of patient 1B.

Patient 4B

Patient 4B, age 23 years, is a sister of patients 1B, 3B, and 5B, and is asymptomatic. Positive physical findings were limited to a grade-II apical and lower left sternal border systolic murmur. The aortic and pulmonic second sounds were of equal intensity. There was no evidence of cardiomegaly or congestive signs. The electrocardiogram was normal and fluoroscopy was not remarkable.

Patient 5B

Patient 5B, age 30 years, is a sister of patients 1B, 3B, and 4B. She has noted shortness of breath with moderate activity and mild substernal distress with exertion for approximately 2 years. She denied syncope but noted lightheadedness with rapid changes in position. She had no antecedent history of rheumatic fever. She has 3 children who are asymptomatic at ages 11, 9, and 7½ years. Her blood pressure was 100/60, heart rate 80 and regular, and respirations 18. Positive physical findings included mild cardiomegaly, the apex impulse being 1 cm. beyond the left midclavicular line in the sixth intercostal space. There was a grade-II systolic murmur along the lower left sternal border

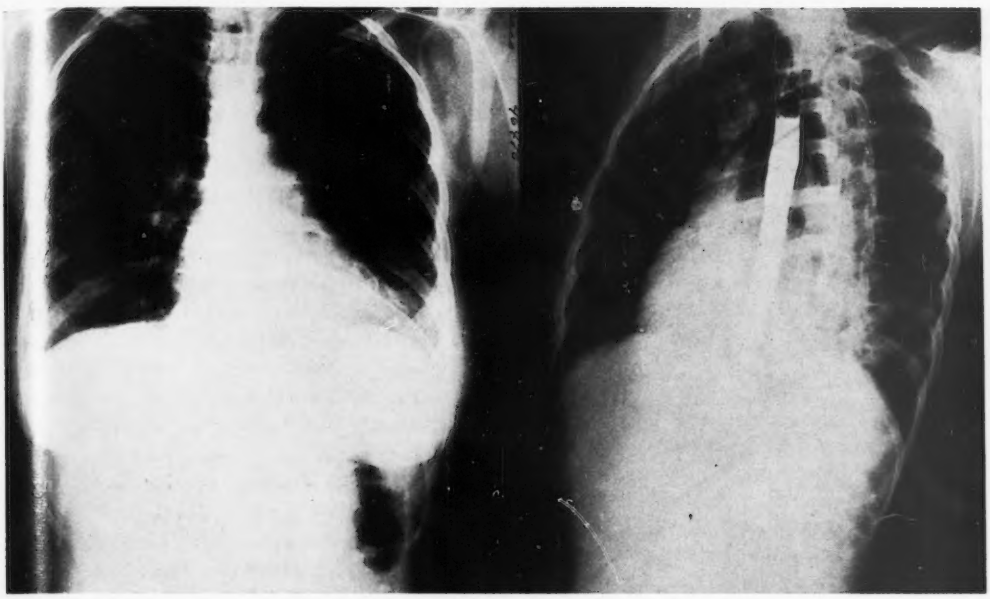

Figure 10

Posteroanterior and left anterior oblique roentgenograms of patient 1B.

and at the apex. The aortic and pulmonic second sounds were normal. The arterial pulses were all of equal intensity. Fluoroscopy revealed the heart to be slightly widened because of left ventricular enlargement. The electrocardiogram demonstrates left ventricular preponderance.

Patient 6B

Patient 6B is the 7½-year-old son of patient 5B. He is asymptomatic. Positive physical findings were limited to a grade-II apical systolic murmur, and slight left ventricular enlargement on fluoroscopy. The electrocardiogram was normal.

The paternal ancestry of patients 1B, 3B, 4B, and 5B has been investigated. The paternal grandfather lived to the age of 65 and died of some type of heart disease. No further history is available. The father died at age 47 of heart disease that had been present almost all of his life. He spent 3 years in a nursing institution following a stroke at the age of 44. A son of his by a previous marriage suddenly dropped dead at the age of 23 (Patient 7B). Another daughter, 24 years of age, has noted shortness of breath on exertion and ease of fatigue. She gives a vague history of rheumatic fever. Her blood pressure was 100/55, heart rate 84 and regular, and respirations 18. The heart was slightly enlarged to the left. There was a grade-III apical systolic murmur that radiated to the axilla. The aortic and pulmonic second sounds were normal. The chest x-ray revealed left atrial and left ventricular enlargement, and the electrocardiogram showed left ventricular preponderance. A retrograde aortic left ventricular catheterization demonstrated no systolic pressure gradient across the left ventricular outflow tract, and rheumatic mitral insufficiency is thought to be present.

A paternal uncle of patient 1B is living at the age of 60, presumably in good health. He has had 7 children, all males, 1 of whom dropped dead at age 18, and 2 more who are thought to have rheumatic heart disease. Another paternal uncle is living in his sixties and has 3 children in good health. The maternal family history has not shown unusual types of heart disease, and the patient's mother has been examined and found to be free of cardiovascular disease.

Discussion

Etiology and Pathophysiology

The exact etiology of familial functional subaortic stenosis is obscure, but structural details suggest an origin different from other lesions of the aortic valve area. Congenital subaortic stenosis of the membranous type is attributed by most authors to persistence of a portion of the bulbus cordis in the outflow tract of the left ventricle.[9, 10] This results in

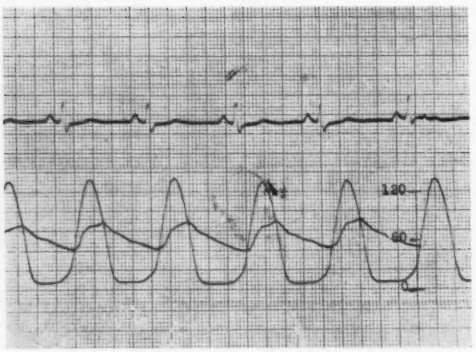

Figure 11

Superimposed, simultaneous pressure tracings obtained in the left ventricle and central aorta in patient 1B.

a membranous obstruction, partially occluding the outflow tract, rather than an extensive area of muscular encroachment.

There are numerous types of myocardial hypertrophy that have been described as clinical entities that can be differentiated either by clinical or pathologic findings. Idiopathic myocardial hypertrophy is characterized by marked cardiomegaly, intractable heart failure, cardiac arrhythmias, tachycardia, and repeated embolic phenomena. Cardiac murmurs or hypertension is not present. At autopsy myocardial hypertrophy and ventricular dilatation are prominent, and subendocardial fibrosis and myocardial degeneration and fibrosis are observed histologically.[11] The signs and symptoms of glycogen-storage disease of the heart become manifest shortly after birth. Initially there is tremendous cardiomegaly with few symptoms. Within months progessive dyspnea and tachycardia develop and sudden death usually occurs within the first year of life. Microscopically, large glycogen deposits in the cardiac and skeletal muscle are predominant.[12] Endocardial fibroelastosis is distinguished by the thickened white endocardium, particularly marked in the left atrium and ventricle. Death at an early age is characteristically preceded by paroxysmal dyspnea, cyanosis, and cardiomegaly.[13] Cardiomegaly has been described in Friedreich's ataxia, more commonly in those with a family history of the disease. Patchy fibrosis and hypertrophy of muscle fibers are the outstanding histologic features.[14] Neurologic features of the disease apparently are present in all those with cardiac enlargement.[15] Several other types of familial cardiomegaly have been described by Evans, Gaunt, and Campbell.[15–17] Tremendous cardiomegaly, arrhythmias, and tachycardia have been characteristic. Patchy fibrosis, hypertrophy, and vacuolization of the muscle fibers have been observed histologically. In none of the above instances has a systolic pressure gradient been recorded across the left ventricular outflow tract, nor in any cases has aortic stenosis, valvular or subvalvular, been suspected clinically.

Some acquired muscular lesions obstructing ventricular outflow have been reported. Engle and co-workers[18] and Brock[19] have described a functional muscular infundibular obstruction of the right ventricular outflow tract that temporarily maintained the systolic pressure gradient following valvotomy in cases of pulmonic valvular stenosis. Morrow et al.[6] reported a case with an analogous, transiently persistent gradient in the subvalvular area of the left ventricle, demonstrated on left heart catheterization 3 weeks after a valvotomy for acquired aortic stenosis. At left heart catheterization 18 months later, this gradient had disappeared. Brock[20] also described the development of a functional left ventricular outflow obstruction in 2 cases, resulting from longstanding hypertensive cardiovascular disease. We have been unable, however, to implicate either valvular disease or systemic hypertension in any of our patients.

Bercu et al.[21] and Morrow et al.[6] have recently described cases similar to our own. Bercu's patient had a severe systolic pressure gradient across the outflow tract of the left ventricle. By means of open-heart surgery with total cardiac bypass, the aortic valves were inspected and found to be normal; and there was no subvalvular membrane. Marked hypertrophy of the musculature of the outflow tract was observed and was presumed to be the cause of the obstruction. The patient subsequently died and at necropsy both ven-

ricles were found to be hypertrophied without apparent cause. Histologic examination was remarkable only for hypertrophy of the individual muscle fibers. An interesting feature of this case is that a brother of the patient underwent transventricular aortic valvotomy for aortic stenosis in 1955 (closed method). He is still living and apparently is clinically improved.

Morrow has had similar experiences with 2 cases in which left heart catheterization had demonstrated subvalvular obstruction warranting surgical relief. At operation, with cardiac bypass and an arrested heart, no obvious obstruction was encountered, either valvular or subvalvular. Again, marked hypertrophy of the musculature of the left ventricular outflow tract was present and presumed to be the cause of the functional obstruction. Later, a functional obstruction of the outflow tract was demonstrated by selective angiocardiography.

In these cases as well as in our own the pathologic physiology can be recognized. The pathologic changes in the heart consist essentially of the tremendous muscular hypertrophy that is particularly marked in the interventricular septum. In the arrested heart at surgery or at autopsy, a finger may be passed with some difficulty from the aorta, past the muscular obstruction, into the left ventricular cavity. Contraction of the muscle during systole in the beating heart causes further obstruction of the outflow tract. The systolic pressure gradient is then due in part to a mechanical muscular component and in part to a functional contracting component. This must be appreciated or the diagnosis could easily be missed, either in the arrested heart at surgery or at autopsy.

No etiologic factor has been apparent. Neither valvular disease nor systemic hypertension can be implicated. The familial incidence of the lesion in our cases strongly implies the likelihood of familial anomaly as the cause; we can only speculate as to its mechanism. The tendency of the musculature of the ventricles to become hypertrophied may be a gradual or an abrupt process, with the terminal stage at any age. A localized hypertrophy in the interventricular septum at the outflow tract may give rise to an obstruction during systolic contraction, which secondarily leads to hypertrophy of the entire left ventricle. A better explanation of the widespread muscular hypertrophy may be found with chemical analysis of the heart muscle. At the present time, the etiology of muscular subaortic stenosis is uncertain, except in those cases secondary to aortic valve disease or systemic hypertension.

Clinical Features

Differential diagnosis of familial functional subaortic stenosis from other varieties of aortic stenosis appears possible. The clinical profile of patients with valvular aortic stenosis, either congenital or acquired, has been well documented by numerous authors.[3, 4, 22, 23] Dyspnea on effort, ease of fatigue, chest pain, and syncope are frequent symptoms of the severe form of this disease. The physical findings include left ventricular enlargement with a vigorous apical thrust, a basal systolic thrill and murmur, and a second aortic heart sound that is either normal or diminished. The typical pulse is described as a small plateau type. The chest x-ray and fluoroscopy usually demonstrate left ventricular enlargement and some degree of dilatation of the ascending aorta. Calcification of the aortic valve is usually present in patients with acquired aortic stenosis over the age of 30 years,[1] and has been reported in congenital valvular and subvalvular stenosis.[24] The electrocardiogram may or may not demonstrate left ventricular preponderance. Pressure recordings show a systolic pressure gradient across the aortic valve area. The cardiac output is usually normal, but in severe aortic stenosis it is fixed and does not rise with exercise.[25] It is the opinion of most authors today that the usual type of congenital subaortic stenosis cannot be distinguished clinically from acquired or congenital valvular stenosis.[3, 7, 24] The presence of an infundibular chamber in subvalvular stenosis may be demonstrated by pressure recordings or on withdrawal of the catheter by cardioangiography.[4, 7]

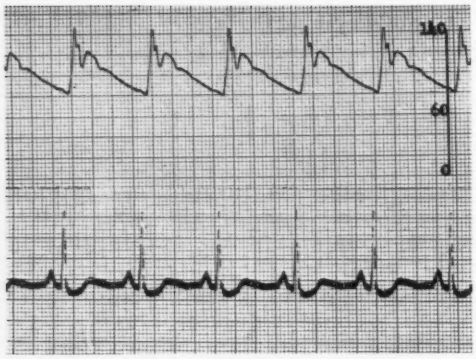

Figure 12

Central aortic pressure tracing in patient 1A demonstrating the widened bisferiens pulse with the rapid systolic upstroke of the initial peak.

It is difficult to distinguish the symptoms of our patients with functional subaortic stenosis from those of acquired aortic valvular stenosis or congenital aortic or subaortic stenosis. Syncope has been the most prevalent complaint among our patients that have been symptomatic, and there has been an alarming incidence of sudden death. However, syncope and sudden death are also common in congenital and acquired aortic stenosis. The physical findings appear to be more helpful. The location of the heart murmur at the apex and in the third and fourth left intercostal spaces adjacent to the sternum has been a constant feature in muscular outflow obstruction, as opposed to the usual basal systolic murmur to the right of the sternum, in valvular stenosis. In no case of muscular subaortic stenosis has the murmur of aortic insufficiency been heard, whereas in congenital valvular and subvalvular stenosis, one third of the patients have an associated murmur of aortic insufficiency.[23] None of our patients had calcification of the aortic valve either on x-ray films or fluoroscopy, and there has been no poststenotic dilatation of the ascending aorta. Pressure recordings during catheter withdrawal may establish the site of the obstruction below the aortic valve; however, they do not distinguish between the usual type of subvalvular stenosis and muscular subaortic stenosis. Angiocardiography has been reported to demonstrate a functional type of outflow obstruction, and perhaps this may permit differentiation.[6]

Another physical sign that may be of diagnostic significance is the widened bisferiens pulse in patient 1A (fig. 12). The initial peak occurs 0.12 second after the R wave and the systolic upstroke duration is 0.07 second. The second peak, occurring 0.24 second after the R wave, is of a much lower pressure. The pulse pressure is 60 mm. of mercury. In severe aortic valvular stenosis, pulsus bisferiens is not uncommon; however, the notch is low on the anacrotic limb and is accompanied by a prolonged systolic upstroke duration and a narrow pulse pressure. The initial peak in patient 1A is most likely due to an ejection of blood early in systole, prior to contraction of the musculature of the left ventricular outflow tract, which causes a functional as well as a mechanical obstruction.

A history implicating other members of the family may be the most significant single clue. Relatives are referred to as having had syncopal attacks, heart murmurs, and sudden death, the latter most frequently in the third decade. Rheumatic valvular disease has been suspected, but in the present reports, a clinical diagnosis of interventricular septal defect has been made in 2 patients who probably have muscular subaortic stenosis.

Familial Aspects of Functional Subaortic Stenosis

The apparent familial incidence of our cases suggests their classification as familial heart disease. Environmental gestational factors as a cause of congenital heart disease have been a source of great interest both in the past and in recent years. In several large series, however, known environmental factors such as rubella and other infections have accounted for only a small percentage of congenital heart disease.[15]

Genetic factors cannot be readily diagnosed. Carleton et al.[26] and Campbell[27] have recently reviewed large series of multiple cases of congenital heart disease occurring in the same families. Although a single gene may not always be the deciding factor, being influenced to some degree by the environment and per-

haps by other genes, they conclude that their material conforms best with a single, recessive, autosomal mode of genetic transmission. Beyond the field of congenital heart disease, there are numerous types of congenital defects based on Mendelian dominant inheritance, i.e., hematologic, neurologic, and connective-tissue disorders. The pedigrees of the family A (fig. 13*A*) and the family B (fig. 13*B*) suggest this type of inheritance. In the absence of consanguinity or of an isolated racial group, which we have excluded to the best of our ability, the appearance of this lesion in 3 generations in large numbers would support this hypothesis. To our knowledge, this is the first series of cases reported that would suggest Mendelian dominant inheritance in familial heart disease.

It should be emphasized that studies on these 2 families have only begun. There are many relatives who have not been examined as yet, mainly because of their scattered places of residence. Another important factor will be the long-term follow-up of members of both families with emphasis on further autopsy and catheterization data. We have already seen that the signs and symptoms can appear early or late in life, and the disease can be of either a malignant or a benign nature.

Therapeutic Aspects

Favorable surgical results similar to those in other types of acquired and congenital aortic stenosis cannot be expected in the treatment of this lesion. This opinion is shared by Brock[20] and Morrow,[6] who have also encountered this problem at surgery. Therefore, the criteria for differential diagnosis must be carefully applied to each candidate for operation for aortic stenosis in order to exclude the inoperable muscular type.

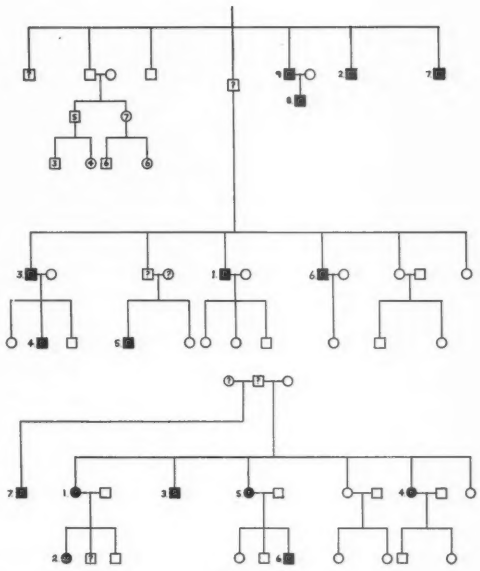

Figure 13

Upper. *Pedigree of family A.* Lower. *Pedigree of family B. The black circles (females) and squares (males) represent involved patients on the basis of (1) clinical, hemodynamic, and autopsy findings, (2) history of heart murmurs and sudden death, or (3) clinical findings. The question marks refer to key persons in the family pedigree, who have not been examined.*

Summary

Two families with familial muscular subaortic stenosis have been studied. Hemodynamic data in 2 cases and the operative findings of 1 case are described. Autopsy findings of 3 cases have been presented. Clinical findings indicate at least 3 additional cases in 1 family and 5 in the other.

The pedigrees of both families have been discussed. The incidence of this lesion in each family over 3 generations suggests that the defect is related to Mendelian dominant inheritance. To our knowledge, this is the first report of cases of familial heart disease compatible with transmission by a Mendelian dominant gene.

The importance of differential diagnosis of this disease from other types of aortic or subaortic stenosis prior to surgery has been stressed, since no operation has been devised for this lesion. The distinguishing clinical features include the apical and lower left sternal border location of the systolic murmur, the absence of poststenotic dilatation of the ascending aorta, the absence of calcification of the aortic valve, the absence of a murmur of aortic insufficiency, and the strong family history suggesting a familial trait.

Summario in Interlingua

Esseva studiate 2 familias con familial stenosis subaortic muscular. Es presentate le datos hemodynamic in 2 casos. Le constatationes operatori in 1 caso es describite. Le constatationes necroptic de 3 casos es presentate. Constatationes clinic indica al minus 3 casos additional in un del familias e 5 in le altere.

Le arbore genealogic de ambe familias es discutite. Le incidentia de iste lesion in cata un del duo familias in le curso de 3 generationes suggere que le defecto es relationate a hereditate per dominante mendelian. Secundo nostre informationes, isto es le prime reporto de casos de congenite morbo cardiac compatibile con transmission per un gen dominante mendelian.

Le importantia del diagnose differential de iste morbo ab altere typos de stenosis aortic o subaortic ante le intervention chirurgic es sublineate, proque nulle operation ha essite elaborate pro iste lesion. Le distinctive characteristicas clinic include le location del murmure systolic al apice e al margine sternal infero-sinistre, le absentia de dilatation poststenotic del aorta ascendente, le absentia de calcification del valvula aortic, le absentia de un murmure de insufficientia aortic, e le marcate historia familial que suggere un tracto familial.

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The Electrocardiogram and Ventricular Gradient in Isolated Congenital Pulmonary Stenosis

By NICHOLAS DEPASQUALE, M.D., AND G. E. BURCH, M.D.

ASPECTS of the electrocardiogram in isolated congenital pulmonary stenosis have been described previously by others.[1-6] This report is concerned with a study of the electrocardiograms and ventricular gradients of 41 patients from the Charity Hospital and Tulane Medical School at New Orleans, Louisiana, who had proved isolated congenital pulmonary stenosis. The diagnoses for the 41 patients were established by cardiac catheterization; 10 were confirmed at surgery and 2 at autopsy.

Methods and Materials

The 41 patients varied in age from 3 to 38 years, the mean being 14 years. Their distribution according to age, sex, and race is shown in table 1. The patients were studied by cardiac catheterization and by conventional clinical and electrocardiographic methods. The electrocardiograms were recorded within 2 or 3 days of cardiac catheterization.

Results

The results are summarized in tables 2 to 4 and figures 1 to 8.

There was electrocardiographic evidence of right ventricular hypertrophy in all but 2 patients and right deviation of the electrical axis of the QRS complex in all patients. Typical examples of 4 types of patterns found are shown in figure 1. In general, however, in all of the electrocardiograms the ratio of the amplitude of the R wave to that of the S wave in lead V_1 was directly related to the pressure recorded in the right ventricle (figs. 2 and 7). The S wave was large and the R wave small in leads recorded to the left of the transition zone, e.g., V_5 and V_6 (fig. 1). The duration of the QRS complex was not affected by age nor by increase in right ventricular pressure.

Table 1

Age, Sex, and Race in Forty-one Cases of Isolated Pulmonary Stenosis

Age				Sex		Race	
0-10	11-20	21-30	31-40	Male	Female	W	N
21	13	4	3	10	23	27	14

The P wave tended to be prominent in leads II, III, and V_1 but its magnitude showed no significant relationship to the pressure recorded in the right ventricle (fig. 3), the correlation coefficient being 0.12.

$\hat{A}_{QRS}$ was oriented to the right in the frontal plane (figs. 4, 5, and table 2). The degree of orientation of $\hat{A}_{QRS}$ to the right in the frontal plane varied directly with the right ventricular systolic pressure (figs. 6 and 7).

$\hat{A}_T$ was oriented more to the left in the frontal plane than $\hat{A}_{QRS}$ (fig. 4, table 2). The angle between $\hat{A}_{QRS}$ and $\hat{A}_T$ was greater than normal in 28 of the 41 patients (68 per cent) due to rightward deviation of $\hat{A}_{QRS}$ without an associated change in $\hat{A}_T$, or to rotation of $\hat{A}_T$ to the left (fig. 4).

$\hat{G}$ had a mean direction in the frontal plane of +65° and a mean magnitude of 54 μv.s., (fig. 4, table 2). The angle between $\hat{A}_{QRS}$ and $\hat{G}$ was greater than normal in 26 patients (63 per cent) (table 3). $\hat{A}_{QRS}$ was located to the right of $\hat{G}$ in 38 of the 41 patients (93 per cent) and to the left of $\hat{G}$ in 3 patients (7 per cent).

Surgical reduction of the pulmonary stenosis resulted in migration of $\hat{A}_{QRS}$, $\hat{A}_T$ and $\hat{G}$ toward normal locations and magnitudes in the frontal plane projection. The only exception was in a patient in whom the right ventricular pressure failed to decrease after surgery (patient 6, table 4). $\hat{A}_{QRS}$ rotated to the left, $\hat{A}_T$ to the right, and $\hat{G}$ to a more normal direction with respect to $\hat{A}_{QRS}$ and $\hat{A}_T$ (table 4, fig. 8). The mean magnitude of $\hat{A}_{QRS}$ de-

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Aided by grants from the U.S. Public Health Service and the Upjohn Company, Kalamazoo, Michigan.

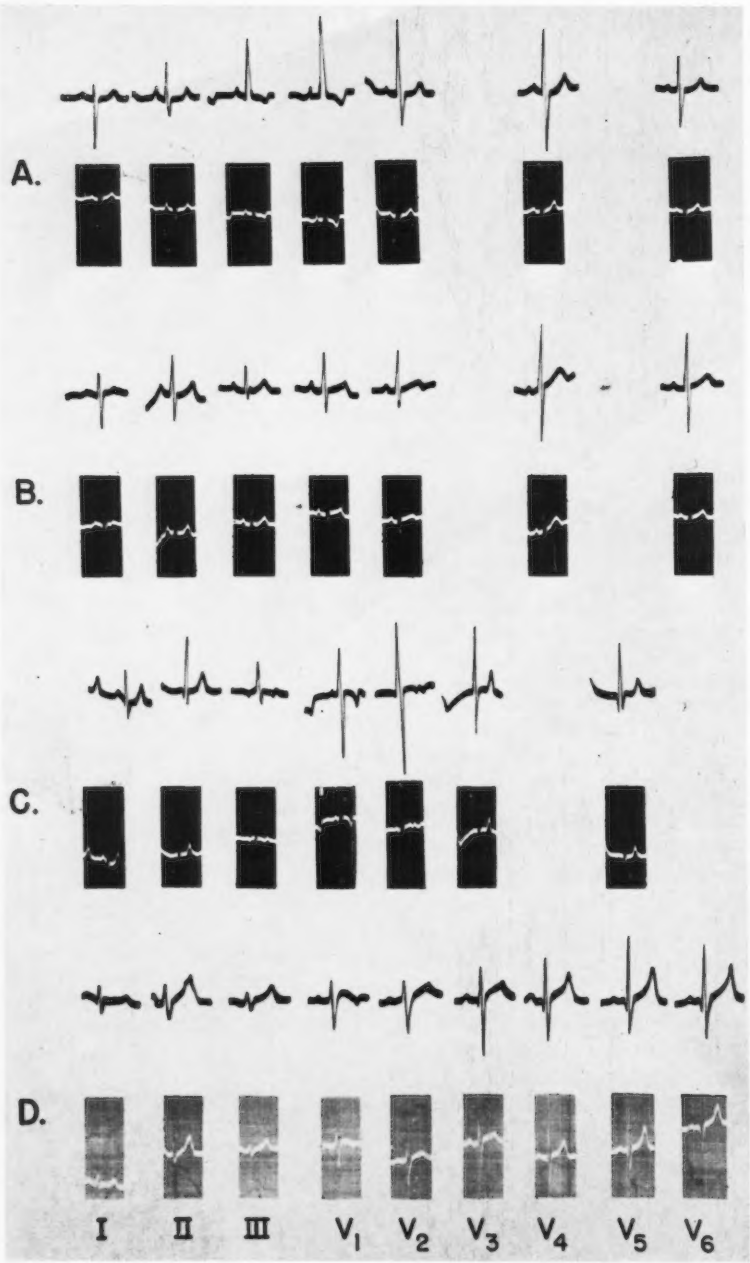

Figure 1

Four types of electrocardiographic patterns in 41 cases of isolated pulmonary stenosis.

Table 2

Electrocardiographic Data in Forty-one Cases of Isolated Pulmonary Stenosis

$\hat{A}_{QRS}$ mean degree	Range degree	Max. mean μV.s.*	Range μV.s.	$\hat{A}_T$ mean degree	Range degree	Max. mean μV.s.	Range μV.s.	$\hat{G}$ mean degree	Range degree	Max. mean μV.s.	Range μV.s.	PR interval mean	QRS duration mean	Height of P_{II} or P_{III} (mm.)† mean	Q in V_1 no. patients	Diphasic P in V_1 no. patients
+128°	+56°, +200‡	31	5,179	+30°	−170°, +91*	48	12,199	+65*	−152°, +160°	54	8,124	.15	.083	1.9	5(12%)	19(46%)

†The lead with the highest P wave was selected.

‡For convenience in calculating mean direction of the vectors and other parameters, when the vector was found to rotate in a clockwise direction beyond 180°, the angle was assigned a positive value. For example, −160° was considered to be +200°.

*Microvolt second.

Table 3

Distribution of Patients According to the Magnitude of the Angle between $\hat{A}_{QRS}$ and $\hat{G}$ and $\hat{G}$ and $\hat{A}_T$

Degrees	A_{QRS}-G (no. cases)	G-A_T
0°-30°	15	28
31°-70°	14	8
>70°	12	5

creased, that of $\hat{G}$ increased, and that of $\hat{A}_T$ remained essentially the same after surgery.

In general, the electrocardiographic patterns found in this congenital anomaly tended to be of 4 types (fig. 1):

Type A

This type of electrocardiogram had a small to absent R wave and a deep S wave in lead I, and a high R wave and a small to absent S wave in lead V_1, and was obtained from patients in whom the right ventricular systolic pressure was greater than 100 mm. of mercury.

Type B

This electrocardiographic pattern was obtained when the right ventricular systolic pressure was between 75 and 100 mm. of mercury. The R wave in lead I was more prominent in type B than in type A but was of less magnitude than the S wave in lead I, whereas the R wave in V_1 was greater in magnitude than the S wave although the S wave in V_1 was moderately deep.

Type C

When the right ventricular systolic pressure was less than 75 mm. of mercury, an electrocardiogram of type C was obtained in which the R wave in lead I was equal to or greater in magnitude than the S wave in lead I and the magnitude of the S wave in V_1 was equal in magnitude to the R wave in V_1.

Type D

This type of tracing was of normal configuration. Two of the 41 patients had a normal electrocardiogram even though the right ventricular systolic pressure was 75 and 105 mm. of mercury, respectively.

Table 4

Electrocardiographic Data before and after Surgical Reduction of Pulmonary Stenosis in Ten Patients

Patient number	Months after surgery	Height of R in V_1 (mm.)		Height of P_{II} or P_{III} (mm.)		$\hat{A}_{QRS}$				$\hat{A}_T$				$\hat{G}$				RV systolic pressure mm. Hg.	
						Before		After		Before		After		Before		After			
		Before	After	Before	After	Location degree	Magnitude μ v.s.	Location degree	Magnitude μ v.s.	Location degree	Magnitude μ v.s.	degree Location	Magnitude μ v.s.	Location degree	Magnitude μ v.s.	Location degree	Magnitude μ v.s.	Before	After
1	53	15	3	1.0	2.0	117	24	110	14	70	54	46	34	84	65	60	40	175	—
2	12	25	10	2.0	2.0	155	62	120	24	0	28	57	44	130	29	82	62	160	35
3	24	16	9	5.5	3.0	193	16	−102	8	−30	44	14	66	−37	51	6	62	165	95
4	24	16	16	1.0	1.0	140	40	120	14	75	60	53	54	101	44	67	64	100	42
5	24	15	16	2.3	2.0	125	38	67	42	65	40	90	30	92	66	76	72	125	103
6	6	22	7	2.0	1.8	103	9	160	6	5	25	91	12	25	26	111	15	90	106
7	48	22	25	1.0	1.8	168	16	63	11	40	26	40	60	69	28	44	72	142	100
8	60	15	4	1.1	2.0	111	45	60	28	60	40	5	32	82	76	29	52	146	30
9	12	7	8	0.7	1.0	129	24	121	42	0	20	25	26	72	20	90	47	105	90
10	48	11	15	2.2	4.0	180	12	−120	23	70	41	6	31	85	40	−54	28	135	—
Mean	31	16	11	1.9	2.0	+142	29	+ 59	21	+35	38	+42	40	+70	44	+51	51	134	75

Figure 2

Relationship of right ventricular systolic pressure to the R/S ratio in lead V_1. When a diphasic R wave was present the highest wave was selected.

Figure 3

Relationship of right ventricular systolic pressure to P wave in lead II or III. The lead with the highest P wave was selected for analysis.

One patient had a right ventricular systolic pressure of 135 mm. of mercury and an electrocardiographic pattern of type C, while another patient had a right ventricular systolic pressure of 69 mm. of mercury and an electrocardiogram of type A.

Discussion

Of the 21 patients whose electrocardiograms were of type A only 1 had a right ventricular systolic pressure of less than 100 mm. of mercury. One other patient, who was 38 years old had a right ventricular systolic pressure of

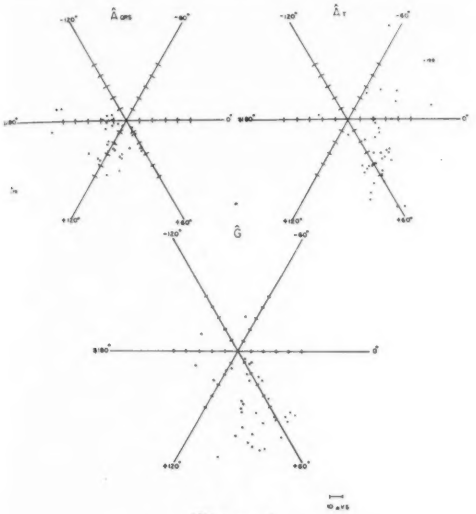

Figure 4

$\hat{A}_{QRS}$, $\hat{A}_T$, and $\hat{G}$ in 41 cases of isolated pulmonary stenosis.

68 mm. of mercury and complete right bundle-branch block. This was the only instance of complete bundle-branch block in this series.

The ventricular gradient of Wilson and associates,[7] an expression of the variations in the duration of the excited state, has been studied by us in patients with congenital and acquired heart disease as well as in normal children.[8-10, 13] Ashman[11] analyzed the electrocardiograms of 164 normal adults and found the mean $\hat{A}_{QRS}$ to have a direction of +41.7° (range, −21.5° to +104.9°) and a mean magnitude of 21.8 μv.s. (40.6 to 3.1 μv.s.) in the frontal plane projection, whereas $\hat{G}$ had a mean direction of +39.2° (+72.2° to +2.2°) and a mean magnitude of 46.2 μv.s. (78.9 to 13.5 μv.s.).* In 77 children (2 to 14 years of age) he found $\hat{A}_{QRS}$ to have a mean direction of +61.1° (+102° to +20.1°) and a mean magnitude of 16.6 μv.s. in the frontal plane projection, whereas in 78 children the $\hat{G}$ had a mean direction of 48.0° (+73.1° to +22.9°) and a mean magnitude of 46.6 μv.s. (72.2 to 16.6 μv.s.). In our study of the ventricular gradients of 172 normal infants and children from birth to 16 years of age,[10] we found that, except for a decrease in the mean magnitude of $\hat{A}_{QRS}$ and to a lesser extent of $\hat{G}$, during the first 3 years of life and a shift of $\hat{A}_{QRS}$ to the right during the first year of life, the values for children were the same as Ashman's values for adults.[11]

*These data were obtained by averaging the values given in Ashman's paper[11] for 80 men and 84 women. The range is equal to twice the average standard deviations.

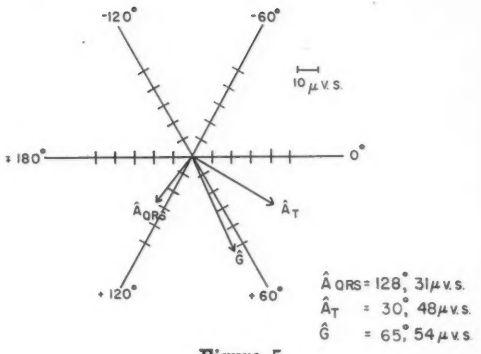

Figure 5

Mean $\hat{A}_{QRS}$, $\hat{A}_T$, and $\hat{G}$ in 41 cases of isolated pulmonary stenosis.

There were abnormally wide angles (>30°) between $\hat{A}_{QRS}$ and $\hat{G}$ in the frontal plane projection in 26 patients (63 per cent) (table 3). In addition, the $\hat{A}_{QRS}$ in 29 patients (71 per cent) was deviated more to the right than the normal (fig. 4), and $\hat{G}$ was abnormal in direction in 22 patients (54 per cent) (fig. 4). The magnitude of $\hat{A}_{QRS}$ was abnormal in 9 patients (22 per cent) and the magnitude of $\hat{G}$ was abnormal in 4 patients (10 per cent). The mean $\hat{G}$: $\hat{A}_{QRS}$ ratio was 2.7; however, in 9 patients the ratio was less than 1.0. In 4 other patients the ratio was greater than 3.0 because of a $\hat{G}$ of unusually great magnitude. Normally, the magnitude of $\hat{G}$ is essentially twice the magnitude of $\hat{A}_{QRS}$.[12]

The abnormal ventricular gradient indicates functional electrical changes in the myocardium other than those due to right ventricular hypertrophy. The ventricular gradient was abnormal in 26 patients (63 per cent), in 22 because of its direction and in 4 because of its magnitude, whereas 39 patients (95 per cent) had electrocardiograms that were not considered to indicate myocardial disease other than ventricular hypertrophy. These

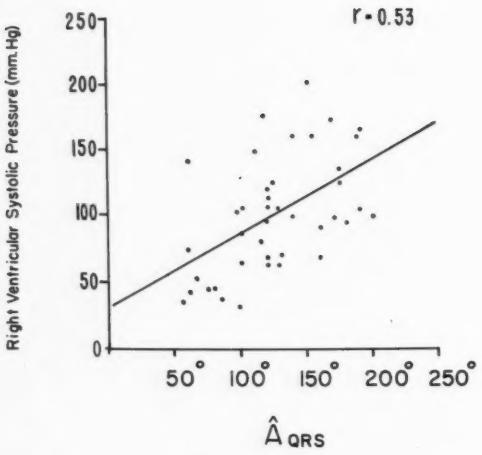

Figure 6

Relationship of electrical position of $\hat{A}_{QRS}$ to right ventricular systolic pressure.

changes apparently are reversible in large part as is indicated by the reversion of the gradient toward the normal following surgery (table 4, fig. 8).

The degree of right ventricular hypertrophy was dependent upon the magnitude of the right ventricular pressure, a finding already indicated by others.[6] The age of the patient was not found to be so important a factor in the production of an abnormal electrocardiogram in congenital pulmonary stenosis as it was in congenital atrial septal defect.[13] Nevertheless, the duration of hypertension in the right ventricle must be a factor of importance in determining the degree of right ventricular hypertrophy. The reason for the absence of a significant relationship of right ventricular hypertrophy to age of the patient is not known.

An interesting aspect of the electrocardiographic pattern in pure pulmonary stenosis was the failure of the QRS complex to become abnormally prolonged with age. Atrial septal defect, on the other hand, is characteristically associated with progressive widening of the QRS complex.[13] The mechanisms responsible for this difference are not clear. In both types of cardiac defects the work of the right ventricle is increased but in atrial septal defect the increase in work is due to an increase in

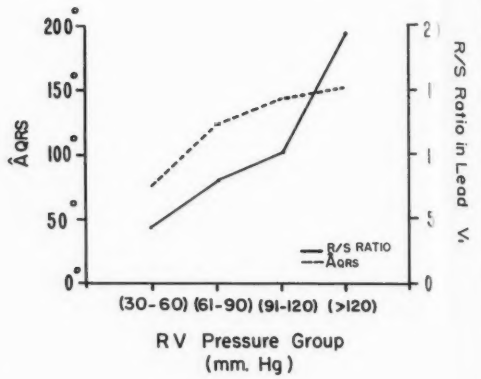

Figure 7

Relationships of R/S^- ratio in V_1 and electrical position of $\hat{A}_{QRS}$ to right ventricular pressure group.

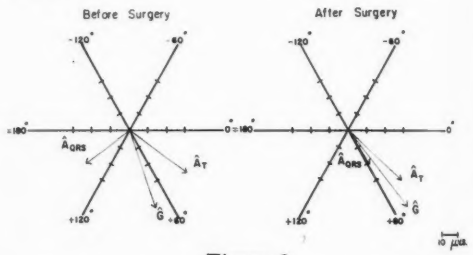

Figure 8

Mean $\hat{A}_{QRS}$, $\hat{A}_T$, and $\hat{G}$ prior to and after surgical reduction of the pulmonary stenosis in 10 patients.

volume output of the heart, whereas in pure pulmonary stenosis the increase in work is due to increase in right ventricular pressure. Anatomically, there is predominantly hypertrophy of the crista supraventricularis in atrial septal defect, whereas in pure pulmonary stenosis there is generalized hypertrophy of the right ventricle. Cabrera and Monroy[14] have already discussed this problem. The precise mechanisms for these differences in anatomic changes remain to be explained. Regardless of the mechanism, these observations demonstrate again the significant relationship of the electrocardiogram to the normal and abnormal functional and anatomic state of the heart.

With the accumulation of more detailed data in future years the role of the electrocardiogram in the clinical diagnosis of congenital cardiac defects should be improved.

Summary

The electrocardiogram and ventricular gradient were studied in 41 patients with isolated congenital pulmonary stenosis. The ventricular gradient was abnormal in 26 of the 41 patients (63 per cent). The $\hat{A}_{QRS}$ migrated to the right in the frontal plane and $\hat{A}_T$ migrated to the left. Following surgical reduction of the stenosis these vectors rotated rapidly toward the normal position.

The electrocardiographic pattern in isolated congenital pulmonary stenosis tended to be of 4 types that were generally related to the right ventricular systolic pressure. The electrocardiographic changes associated with this defect, in which the work of the right ventricle was increased because of right ventricular hypertension, were different from those associated with atrial septal defect in which right ventricular work was increased because of high volume output. The duration of the QRS complex was not prolonged in the electrocardiograms of patients with pulmonary stenosis, whereas it was characteristically prolonged in those with atrial septal defect.

Summario in Interlingua

Le electrocardiogramma e le gradiente ventricular esseva studiate in 41 patientes con isolate congenite stenosis pulmonar. Le gradiente ventricular esseva anormal in 26 del 41 (63 pro cento). A_{QRS} migrava verso le dextera in le plano frontal, e A_T migrava verso le sinistra. Post reduction chirurgic del stenosis, iste vectores rotava rapidemente verso lor positiones normal.

Le patrono electrocardiographic in isolate congenite stenosis pulmonar tendeva a gruppar se in un de 4 typos que esseva generalmente relationate al tension systolic dextero-ventricular. Le alterationes electrocardiographic associate con iste defecto, in que le labor del ventriculo dextere esseva augmentate a causa del presentia de hypertension dextero-ventricular differeva ab le alterationes electrocardiographic associate con defecto atrio-septal in que le labor del ventriculo dextere esseva augmentate a causa de un alte volumine del rendimento. Le duration del complexo QRS non esseva prolongate in le electrocardiogrammas de patientes con stenosis pulmonar, durante que illo esseva characteristicamente prolongate in patientes con defecto atrio-septal.

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Arteriosclerosis Obliterans:

Review of 520 Cases with Special Reference to Pathogenic and Prognostic Factors

By JOHN L. JUERGENS, M.D., NELSON W. BARKER, M.D., AND EDGAR A. HINES, JR., M.D.

THE diagnostic term "arteriosclerosis obliterans" denotes a degenerative arteriopathy of the extremities and of the aorta and its branches that go to the extremities. It is characterized by occlusive lesions consisting primarily of atheromas, which are often accompanied by fibrosis and calcification of the medial coat of the artery and which may be associated with thrombosis of varying extent. In the past, arteriosclerosis obliterans has been considered to be an occlusive arterial disease affecting predominantly older people and patients with diabetes mellitus. There is a general clinical impression, however, that the disease is now being recognized more frequently in younger nondiabetic patients just as is atherosclerosis of the coronary arteries.

This study is based on a review of the records and a follow-up of a group of 520 nondiabetic patients who were less than 60 years of age at the time a clinical diagnosis of arteriosclerosis obliterans was made and who had had at least one determination of plasma cholesterol. The younger age groups were selected for study because mild arteriosclerosis obliterans is such a frequent incidental finding in older patients that if a large proportion of these with all their other infirmities were to be included, the prognostic and pathogenic factors of arteriosclerosis obliterans would be difficult to assess. Nondiabetic patients were selected because diabetes mellitus frequently accelerates the atherosclerotic process and may thus distort the clinical course of arteriosclerosis obliterans. Patients with plasma cholesterol determinations were selected because we hoped to learn whether the concentration of cholesterol is an important factor in the prognosis and pathogenesis of arteriosclerosis obliterans.

The purpose of this study was 3-fold. First, in view of the great current interest in the problem of the pathogenesis of atherosclerosis, we hoped that some information concerning this problem might be obtained from a clinical review of a fairly large series of patients with symptomatic atherosclerosis of the extremities. Second, we thought that information might be obtained regarding factors that influence the prognosis as to life and preservation of limbs of these patients. Third, since the patients in this series were treated before the era of direct arterial surgery for chronic occlusive arterial disease, we thought that information regarding the prognosis as to life and limb might be useful as a base line for comparison with such information from other groups of similar patients, many of whom are currently being treated by surgical procedures designed to restore arterial continuity.

Material and Method

The Mayo Clinic records of all nondiabetic patients less than 60 years of age who received a clinical diagnosis of arteriosclerosis obliterans during the 10-year period 1939 through 1948 were reviewed. The diagnosis in each case had been verified by one of the consultants who had a special interest in peripheral vascular diseases. Other occlusive arterial diseases such as thromboangiitis obliterans, arterial embolization, and simple arterial thrombosis were excluded, and if the diagnosis was in doubt, the case was discarded. All patients had one or more determinations of plasma cholesterol available for review; usually only one value was available, but in the occasional case in which there was more than one value the average value was used.

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Follow-up information was obtained from the records of subsequent visits of the patients to the clinic and from answers to letters sent them in 1957. Questions were asked regarding the state of the patient's general health, subsequent surgical procedures performed elsewhere for the treatment of their arterial disease, and their smoking habits. If the patient died, information was sought as to the cause of death. Of the 520 patients selected for study, 471 patients (91.6 per cent) were traced for 3 years and 464 patients (89.2 per cent) were traced for 5 years following the initial diagnosis at the clinic. Of the 383 patients who could have survived for 10 years, 334 (87.2 per cent) were traced.

The criteria for the clinical diagnosis of arteriosclerosis obliterans were those commonly accepted in clinical practice and stated by Allen, Barker, and Hines.[1] It has been found that clinical diagnosis based on these criteria has been confirmed with very few exceptions when the affected arteries obtained from amputation specimens or at necropsy have been examined histopathologically. All of the patients in this study had intermittent claudication and marked diminution or absence of pulsations in one or both of the femoral arteries in Scarpa's triangle or in one or both of the popliteal arteries in the popliteal space; many patients had objective or subjective manifestations of ischemia of the toes or feet.

Angiographic examination was not done. Although the proximal points of arterial occlusion can be determined with certainty only by angiographic means or by surgical exploration, a careful appraisal of the arterial pulsations and an evaluation of the patient's symptoms give a reasonably accurate idea of the proximal site of arterial occlusion. For example, if popliteal arterial pulsations are normal but posterior tibial and dorsalis pedis arterial pulsations at the ankle level are absent, it is reasonably certain that the proximal occlusion is in the tibial arteries. If the popliteal arterial pulsation is absent but the femoral pulsation in Scarpa's triangle is normal, the proximal level of occlusion is in the femoral artery in the thigh. If one femoral arterial pulsation is normal and the other one is absent, the common or external iliac artery is occluded on the side where the femoral pulsation is absent, but the iliac artery on the other side is open. When both femoral arterial pulsations are markedly impaired or absent, both iliac arteries or the abdominal aorta or all 3 are occluded.

In the present study, the patients were divided into 2 groups on the basis of the location of the arterial occlusion as indicated by appraisal of the arterial pulsations. These groups were designated respectively "femoral" and "aorto-iliac." There are patients in each group with clinical evidence of unilateral or bilateral occlusion. No significant differences were noted for some of the factors that were analyzed in the 2 groups; where differences were noted, they are mentioned.

Some Factors of Possible Significance in Pathogenesis

Sex

Of the entire group of 520 patients, all white, 478 were men and 42 were women, giving a male-to-female ratio of approximately 11 to 1. This ratio is greater than that usually reported for white patients in this age group who have clinical evidence of coronary atherosclerosis; it tends to approach, but does not equal, the even more striking male preponderance in thromboangiitis obliterans in which the ratio of males to females is usually given as approximately 50 to 1. It is likely that the normal secretion of estrogens by the premenopausal woman tends to protect against atherosclerosis of the arteries of the lower extremities just as it seems to protect against atherosclerosis of the coronary arteries. This protection may extend for several years after the menopause, as far as clinical manifestations of the disease are concerned. It is noteworthy that only 3 of the 42 women in this series were menstruating at the time the clinical diagnosis of arteriosclerosis obliterans was made, and that 33 of the 42 women (78.6 per cent) were in the age group 50 to 59 years.

Plasma Cholesterol

The concentration of plasma cholesterol was determined in all patients (table 1). For purposes of comparison, data similar to those for the study group are presented for 2 control groups of nondiabetic male patients whose ages ranged from 40 to 60 years and who had no clinical evidence of atherosclerosis of the coronary or peripheral arteries. One of the control groups consisted of 100 ambulatory Mayo Clinic patients and another group consisted of 94 patients confined to the Rochester State Hospital because of emotional disturbances or organic disease of the brain not considered to be due to atherosclerosis. All of the

Table 1

Values of Plasma Cholesterol in Patients with Arteriosclerosis obliterans and in Two Control Groups

Group	Patients	Cholesterol, mg. per 100 ml. of plasma		
		Range	Mean	Standard deviation
Patients with arteriosclerosis obliterans				
Total	520	103-642	256.3	55.8
Female	42	151-642	289.8	81.3
Male	478	103-630	253.4	53.2
Control patients				
Mayo Clinic	100	144-278	198.4	24.9
Rochester State Hospital	94	120-331	202.9	37.3

latter group were moderately active physically and consumed a diet containing an average of 125 Gm. of fat and 2,800 calories daily. All determinations of plasma cholesterol were made in a Mayo Clinic laboratory.

The mean concentration of plasma cholesterol in men with arteriosclerosis obliterans was approximately 50 mg. per 100 ml. higher than that of either of the 2 control groups of men. Because of the relatively small number of women in this study, no comparisons were attempted with a control group of women, but it is noteworthy that the mean concentration of plasma cholesterol in the women with arteriosclerosis obliterans was approximately 35 mg. per 100 ml. higher than that of the men with this disease. It was 250 mg. per 100 ml. or greater in 48 per cent of the men and 74 per cent of the women with arteriosclerosis obliterans but in only 5 per cent of the Mayo Clinic controls and 8 per cent of the Rochester State Hospital controls with no clinical evidence of arteriosclerosis.

As in other similar studies on patients with disease of the coronary arteries, there is a considerable overlap of cholesterol values between patients with arteriosclerosis obliterans and the 2 control groups, and it is apparent that there is a significant number of patients with arteriosclerosis obliterans whose values for plasma cholesterol can be considered within the normal range.

Tobacco Smoking

Information as to the incidence and extent of tobacco smoking was available on 401 of the 478 men. This factor was tabulated on the basis of the amount of smoking at the time of onset of symptoms, since some of the patients had stopped smoking before coming to the clinic. It is of interest that at the onset of symptoms of arteriosclerosis obliterans, 97.5 per cent of the men were smokers and 33 per cent smoked 20 or more cigarettes a day. For purposes of comparison, data on the smoking habits of 350 Mayo Clinic male patients between the ages of 25 and 55 years with no evidence of vascular disease were available.[2] In this control group, 26 per cent were nonsmokers and 33 per cent smoked 20 cigarettes or more a day. On the assumption that these 2 series of patients are comparable, the incidence of smoking in men less than 60 years of age who had arteriosclerosis obliterans was significantly higher than in those patients who did not have evidence of this disease; however, the incidence of heavy smoking was no higher in the study group than in the control group.

We were impressed by the fact that only 2.5 per cent of the male patients with arteriosclerosis obliterans were nonsmokers. This is almost as small an incidence of nonsmoking as has been previously reported in patients with thromboangiitis obliterans, also an occlusive peripheral arterial disease. This suggests that tobacco smoking may produce some sort of peripheral arterial injury and may be a factor in the localization of atherosclerosis in a certain small group of susceptible individuals. It is also possible that in some patients with atherosclerosis, tobacco smoking may be a factor in the secondary arterial thrombosis that occurs.

Obesity

In some series, obesity has been considered to be a contributing factor in the pathogenesis of coronary atherosclerosis, but in our series of patients with arteriosclerosis obliterans obesity was relatively uncommon. With a weight of more than 200 pounds in men and

of more than 175 pounds in women used as an index of obesity, only 5 per cent of our patients were obese. This rather arbitrary criterion of obesity without regard to the patients' height or body build is subject to some error in interpretation, but we believe that it gives a rough index of the incidence of obesity. In the control group of 100 ambulatory male patients who were 40 to 60 years of age and who had no clinical evidence of atherosclerosis, 15 patients weighed more than 200 pounds. Thus, it would appear that in middle-aged nondiabetic patients obesity is not commonly associated with arteriosclerosis obliterans and probably is not a significant factor in the pathogenesis.

Hypertension

Since hypertension has been considered to be at least an accelerating factor in the pathogenesis of atherosclerosis, particularly in coronary atherosclerosis, we studied our group of patients from this standpoint. We found that 25 per cent of the study group had blood pressures greater than the arbitrary values of 150 mm. of mercury systolic and 90 mm. diastolic chosen as the upper limits of normal, as compared to 9 per cent in the control group of 100 male patients. It is evident, therefore, that the incidence of hypertension according to these criteria is significantly higher in the group of patients with arteriosclerosis obliterans than in the control group. It is noteworthy that almost three fourths of the patients with arteriosclerosis obliterans did not have hypertension. It would appear that in patients with arteriosclerosis obliterans, hypertension cannot be considered a frequent accelerating factor in the disease process.

Symptoms and Complications at the Time of Diagnosis (Table 2)

All 520 patients had a history of intermittent claudication in one or both lower extremities. This was the only symptom of occlusive arterial disease in 380 patients (73.1 per cent). Eighty-five patients (16.3 per cent) also had pain that was interpreted as rest pain due to local tissue ischemia or pain due to ischemic neuropathy of larger nerve trunks. Fifty-five patients (10.6 per cent) had ischemic ulceration or gangrene. A number of these patients with ulceration or gangrene also complained of ischemic rest pain or had ischemic neuropathy but for convenience were categorized as having only ulceration or gangrene. The incidence of rest pain, neuropathy, ulceration, and gangrene was greater in the patients whose proximal arterial occlusion was in the femoral artery than in those whose occlusion was in the aorto-iliac vessels.

There was a history of previous myocardial infarction or chest pain consistent with angina pectoris in 16 per cent of the entire group. This relatively high incidence of the clinical manifestations of coronary arteriosclerosis is not surprising, since both coronary arteriosclerosis and arteriosclerosis obliterans are similar pathologic conditions affecting arteries and both can be considered to be complications of atherosclerosis in general. The incidence of clinical coronary arteriosclerosis is somewhat greater in patients with occlusion of the femoral artery than in patients with aorto-iliac involvement.

Table 2

Symptoms and Complications in 520 Patients at Time of Diagnosis of Arteriosclerosis Obliterans at Mayo Clinic

Symptom or complication	Patients with: Femoral artery occlusion (296) Number	Per cent	Aortic-iliac occlusion (224) Number	Per cent	Arteriosclerosis obliterans (total 520) Number	Per cent
Intermittent claudication only	201	67.9	179	79.9	380	73.1
Ischemic rest pain, ischemic neuropathy, or both	53	17.9	32	14.3	85	16.3
Ischemic ulceration, gangrene or both	42	14.2	13	5.8	55	10.6
Coronary artery disease (infarction or angina)	56	18.9	27	12.1	83	16.0

Table 3

Survival Rates for Patients with Femoral Artery and Aorto-iliac Occlusion

Site of occlusion	Survival period, years	Patients: Total	Patients: Traced	Lived beyond indicated period: Number	Lived beyond indicated period: Per cent*
Femoral artery	3	296	272	234	86.0
	5	296	271	217	80.1
	10	221	201	115	57.2
Aorto-iliac region	3	224	199	163	81.9
	5	224	193	141	73.1
	10	162	133	62	46.6

*Based on traced patients. Inquiry as of January 1, 1957. The 10-year group includes only those patients with a diagnosis of arteriosclerosis obliterans prior to 1947.

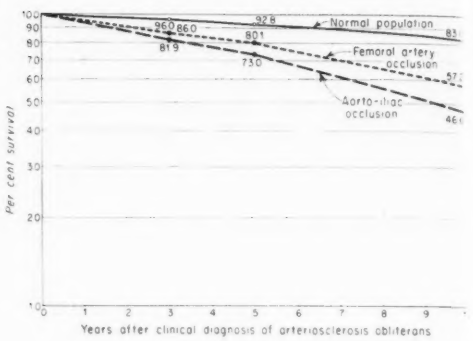

Figure 1

Survival rates for patients with atherosclerotic aorto-iliac occlusion and femoral artery occlusion compared with survival rates for a normal population of the same age and sex distribution.

Treatment

In general, the following basic regimen was recommended for all patients. They were advised to discontinue the use of tobacco and to protect their feet carefully from any type of injury, whether mechanical, thermal, or chemical. Patients with increased plasma cholesterol were for the most part instructed in the use of a diet low in fat content and advised to adhere to this diet. Many who had intermittent claudication as the only clinical manifestation were given one or more courses of intramuscular injections of deproteinated pancreatic extract. Most patients who had ischemic rest pain, ischemic neuropathy, or ischemic ulcers or gangrene were treated for varying periods in the hospital with rest, an oscillating bed, and frequently with vasodilating drugs. In 44 of these patients, unilateral or bilateral surgical lumbar sympathetic ganglionectomy was performed. Gangrene was found to be extensive and unresponsive to conservative treatment in 21 of the 520 patients (4 per cent) and amputation of the leg was performed on these patients soon after their original examination. Only 2 per cent of the patients with aorto-iliac disease required amputation of the leg at the time of their first visit while 5 per cent of those with involvement of the femoral artery required amputation at that time.

Prognosis

Survival Rates

Survival rates, given in table 3, were calculated by the direct method[3] separately for the group of patients whose proximal point of occlusion was in the aorto-iliac vessels and for the group whose proximal point of occlusion was in the femoral artery. There rates are shown graphically in figure 1 and are compared with those of a general population of the same age and sex distribution. The survival rate for the traced patients is significantly lower than that for the general population, and the survival rate for the group with aorto-iliac occlusion is less favorable than that for the group with femoral-artery occlusion. The cause of death could not always be determined with accuracy, but in 76 patients, or approximately three fourths of those known to have died in the follow-up period, the cause of death was probably arteriosclerosis of the coronary arteries, that is, the death was reported to be due to a "heart attack" or "heart disease" or was a sudden death presumably due to heart disease.

Some of the factors that might have influenced the prognosis of this disease are given

Table 4

Five-Year Survival Rates Following Original Diagnosis at Mayo Clinic*

Category of patient at time of diagnosis	Patients with: Femoral artery occlusion			Aorto-iliac occlusion			Arteriosclerosis obliterans (total)		
		Lived beyond 5-year period			Lived beyond 5-year period			Lived beyond 5-year period	
	Traced	Number	Per cent	Traced	Number	Per cent	Traced	Number	Per cent
All patients	271	217	80.1	193	141	73.1	464	358	77.2
Without clinical coronary artery disease	225	189	84.0	169	128	75.7	394	317	80.5
With coronary artery disease (infarction or angina)	46	28	60.9	24	13	54.2	70	41	58.6
Cerebrovascular accident	13	7	53.8	5	4	80.0	18	11	61.1
Hypertension (more than 150/90)	70	53	75.7	46	31	67.4	116	84	72.4
Plasma cholesterol, mg./100 ml.									
Less than 250	137	107	78.1	98	70	71.4	235	177	75.3
250 or more	134	110	82.1	95	71	74.7	229	181	79.0

*Based on traced patients. Inquiry as of January 1, 1957. Includes only those patients with a diagnosis of arteriosclerosis obliterans prior to 1952.

in table 4. It will be noted that the 5-year survival rate is significantly lower for the patients who had clinical coronary arteriosclerosis and for those who had had a cerebrovascular accident than for those who did not. In another study of the prognosis for patients who had survived an initial myocardial infarction by 1 month or more, the 5-year survival rate was found to be 55 per cent.[4] Thus, we believe that the survival rate for patients with arteriosclerosis obliterans and clinical disease of the coronary arteries is approximately the same as that for patients with clinical coronary disease who do not have arteriosclerosis obliterans of the lower extremities.

The 5-year survival rate for patients whose blood pressure was more than 150/90 is only slightly lower than the rate for the entire group. Although the concentration of plasma cholesterol may be of significance in the pathogenesis of atherosclerosis, we could find no correlation between the cholesterol concentration and the survival of our patients with arteriosclerosis obliterans.

Subsequent Amputation of Leg

As previously mentioned, 21 of the 520 patients (4 per cent) required amputation of a leg soon after their original examination at the clinic. From information obtained at subsequent examinations and from the follow-up letters we determined that the incidence of subsequent amputations during the 5-year period following the original examination and diagnosis was 4.9 per cent for the total 465 traced patients, only 3.0 per cent for those with intermittent claudication as the only symptom, 3.8 per cent for those with more severe degrees of ischemia as manifested by rest pain or ischemic neuropathy, and 19.6 per cent for those with gangrene or ulceration (table 5). Our data indicate that ischemic ulceration or gangrene is of more serious import, insofar as survival of an extremity is concerned, when the proximal site of occlusion is in the femoral artery than when it is in the aorto-iliac region.

Of 159 traced patients who smoked at the time of diagnosis and who survived 5 years,

Table 5

Subsequent Amputations of Leg within Five Years of Original Diagnosis at Mayo Clinic

Category of patient at time of diagnosis	Patients with: Femoral artery occlusion			Aorto-iliac occlusion			Arteriosclerosis obliterans (total)		
		Amputation within 5 years			Amputation within 5 years			Amputation within 5 years	
	Traced	Number	Per cent	Traced	Number	Per cent	Traced	Number	Per cent
All patients	271	15	5.5	194*	8	4.1	465	23	4.9
Claudication only	180	5	2.8	156	5	3.2	336	10	3.0
Ischemic rest pain, neuropathy, or both	50	1	2.0	28	2	7.1	78	3	3.8
Ischemic ulceration, gangrene, or both	41	9	22.0	10	1	10.0	51	10	19.6
Smokers who continued to smoke	54	8	14.8	34	2	5.9	88	10	11.4
Smokers who abstained from smoking	49	0	0	22	0	0	71	0	0

*Includes one patient who subsequently was lost to calculation of 5-year survival rate.

88 had continued to smoke and 71 had abstained from smoking after the diagnosis was made. It is of some interest that 11.4 per cent of all who continued to smoke required an amputation within the 5-year period while none who abstained from smoking required amputation during this period.

Summary

The clinical and follow-up data on 520 nondiabetic patients less than 60 years of age who had a clinical diagnosis of arteriosclerosis obliterans of the lower extremities made at the Mayo Clinic in the period 1939 through 1948 were reviewed from the standpoint of pathogenesis, prognosis, and clinical course of the disease. The ratio of males to females was 11 to 1, and the mean concentration of plasma cholesterol in the male patients with arteriosclerosis obliterans was approximately 50 mg. per 100 ml. greater than that of either of 2 control groups of men without clinical evidence of atherosclerosis. The incidence of smoking among the men with this disease was higher than in a comparable group of men without it. Obesity was not commonly associated with arteriosclerosis obliterans, while hypertension was associated with the disease about 3 times as often as in a control group without the disease.

The survival rate for patients with arteriosclerosis obliterans was less favorable than that of a normal population of a similar age and sex distribution, and the survival rate for patients with atherosclerotic aorto-iliac occlusion was significantly less favorable than that of patients with atherosclerotic occlusion of the femoral artery. In approximately three fourths of the patients who died, the cause of death was thought to be disease of the coronary arteries. The presence of atherosclerosis elsewhere than in the arteries supplying the extremities, as manifested by clinical coronary artery or cerebrovascular disease at the time of diagnosis, had an adverse effect on survival.

Four per cent of the patients required amputation of a leg shortly after the diagnosis of arteriosclerosis obliterans was made at the clinic, and an additional 4.9 per cent subsequently required amputation during the 5-year period following the initial examination. Only 3.0 per cent of patients with intermittent claudication as the only symptom of their disease required an amputation during this period. Eleven and three-tenths per cent of patients who continued to smoke, but none who abstained from smoking, had amputations within 5 years.

Since all patients of the series were treated before the advent of direct arterial surgery for segmental arterial occlusion, it is believed that the subsequent course of the disease in these patients may be used as a basis for comparative evaluation of results in patients subjected to direct arterial surgical procedures.

Summario in Interlingua

Esseva revistate—ab le puncto de vista del pathogenese, del prognose, e del curso clinic del morbo—le dossiers de datos clinic e de observationes de controlo posterior in le casos de 520 patientes non-diabetic de minus que 60 annos de etate in qui le diagnose clinic de arteriosclerosis obliterante del extremitates inferior esseva establite al Clinica Mayo durante le annos ab 1939 usque al fin de 1948. Le proportion de masculos a femininas esseva 11 a 1, e le concentration medie del cholesterol plasmatic in le patientes masculo con arteriosclerosis obliterante esseva circa 50 mg per 100 ml que illo del un e del altere de 2 gruppos de controlo de masculos sin evidentia clinic de atherosclerosis. Le incidentia del habitude del fumar inter le masculos con le morbo esseva plus alte que in un gruppo comparabile de masculos sin ille morbo. Obesitate non esseva communmente associate con arteriosclerosis obliterante, durante que hypertension esseva presente in le gruppo con le morbo con un frequentia de circa 3 vices le frequentia de illo in un gruppo de controlo de masculos sin le morbo.

Le cifras de superviventia pro patientes con arteriosclerosis oblitterante esseva significativemente minus favorabile que illos de un population normal de comparabile etates e distribution sexual, sed le cifras de superviventia pro le patientes con atheroscleroticc occlusion aorto-iliac monstra iste tendentia disfavorabile plus marcatemente que illos pro le patientes con occlusion atheroscleroticc del arteria femoral. In approximativemente tres quartos del patientes qui moriva, le causa de morte esseva vidite in morbo de arteria coronari. Le presentia de atherosclerosis in partes altere que le arterias alimentante le extremitates e manifeste in morbo clinic coronario-arterial o cerebrovascular al tempore del diagnose habeva un effecto adverse super le duration del superviventia.

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Vesalius

Who was Andreas Vesalius, and why did his book mark an epoch?

He was born at Brussels at midnight as the last day of 1514 was passing into the first of 1515. His family, which had dwelt for several generations at Nymwegen and which originally bore the name of Witing, had produced many doctors and learned men, and his father was apothecary to Charles V. His mother, to judge by her maiden name, Isabella Crabbe, was probably of English extraction.

The young Vesalius (or Wesalius, for so it was sometimes spelt) was sent to school at Louvain and afterwards entered the University there, which then as later was of great renown. Though he diligently pursued the ordinary classical and rhetorical studies of the place, the bent of his mind early shewed itself; while yet a boy he began to dissect such animals as he could lay his hands on. Such a boy could not do otherwise than study medicine, and in 1533, a lad of seventeen or eighteen, he went to Paris to sit at the feet of Sylvius, then rising into fame.—Sir M. Foster, *Lectures on the History of Physiology.* London, Cambridge University Press, 1901.

Abnormal Electrocardiograms in Apparently Healthy People

I. Long Term Follow-up Study

By F. A. L. Mathewson, M.D., and G. S. Varnam, M.D.

IT has been largely in connection with known or suspected illness that the electrocardiogram in conjunction with other clinical and laboratory evidence has proved a reliable diagnostic aid. Because coronary artery disease in its early stages may run a clinically silent course, the scope of electrocardiography has been extended to include the examination of apparently healthy people on the hypothesis that its routine use may reveal the presence of coronary artery disease in a manner analogous to the detection of early tuberculosis by x-ray examination of the chest. It is now customary for the physician to include an electrocardiogram in the periodic health examination of asymptomatic people. It forms part of the regular health examinations of military personnel, particularly those in the Air Forces, and is one of the requirements for large amount applications for life insurance. In industry, the periodic examination of employees, particularly men over the age of 40 in the executive class, calls for an electrocardiogram whether or not there are symptoms suggestive of heart disease. In Canada the Department of Transport, in the interest of public safety, requires pilots to have an electrocardiogram at stated intervals. In these situations the so-called "abnormal" electrocardiogram is assessed as an isolated finding without the support of confirmatory evidence. Because the suspicion of heart disease, particularly coronary artery disease, may have a far-reaching effect upon the individual, it is important to identify beyond any reasonable doubt the clinical significance of those variants that appear in the electrocardiograms of apparently healthy people.

This problem was brought clearly into focus in the Royal Canadian Air Force during World War II when examples of partial heart block, bundle-branch block, and a variety of unusual T-wave changes were found in the routine electrocardiograms of some apparently healthy pilots and air crew trainees.[1-3] The Department of Transport in Canada also experienced the same problem in 1944, when it initiated a program of routine electrocardiograms for civilian pilots. Similar experiences were reported elsewhere.[4-6] More urgent matters required attention at that time but it was clear that a long-term follow-up study would be necessary to settle this problem. This project was therefore undertaken in 1946 while it was still possible to contact many of the pilots who were examined during the war years. Electrocardiograms and clinical examinations on such a group repeated over a period of years would establish within reasonable limits the uses and limitations of the routine electrocardiogram as a diagnostic procedure, particularly with respect to its ability to identify otherwise silent coronary artery disease.

It is the purpose of this report to present the results of the first analysis of follow-up data pertaining to 3,983 military and civilian pilots whose original electrocardiograms and medical examinations were recorded between the years 1940 and 1948. It is divided into 2 parts. After presenting the scope of the study and the general characteristics of the population, Part I shows the distribution of normal and abnormal electrocardiograms on entry

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Presented in part at the Third World Congress of Cardiology held in Brussels, Belgium, September 1958.

This study is supported by Grant No. 8810-02 of the Defence Research Board, Department of National Defence, Ottawa, Canada.

and at the time of the most recent examination. It includes also the mean age, exposure, deaths, and cardiovascular morbidity to date for each class of observed electrocardiographic abnormality. It does not describe in detail the characteristics of specific electrocardiographic variants. Such reports are published separately.[7-9] Based upon the analysis of the electrocardiograms of the 32 subjects who developed clinical evidence of myocardial disease, Part II shows to what extent the routine electrocardiogram was of value, both as a predictive and a diagnostic test.

Material and Procedure

The subjects in this study were drawn from 3 sources: 1. In the early years of World War II, as a part of a broad study of aircrew-selection methods in the R.C.A.F., electrocardiograms were recorded on several thousand cadets during their pre-flight training. Most of these men graduated as aircrew and served in this capacity during the war. 2. At approximately the same time R.C.A.F. pilots aged 35 and over were required to have electrocardiograms at the time of their annual examination for flying fitness. Except for an older age distribution, these subjects resembled those in the first group. 3. Since 1944 in Canada commercial pilots have been required to submit an electrocardiogram every third year as a condition of license renewal. Since these people meet the physical requirements for flying, they are essentially similar to those examined in the service; in fact, the majority of civilian pilots in the postwar years were ex-R.C.A.F. pilots whose original records were taken in the service.

All subjects were fit for flying duties when their initial electrocardiograms were recorded. Because of the cost of flying training and the physiologic demands of flight, the health requirements for flying usually are interpreted more rigidly than for other occupations but minor clinical variants, which are not thought to impair function or to interfere with longevity, do not prevent a candidate from being classified as fit. Note was made of all subjects who, on entry, gave a history of scarlet or rheumatic fever (16 per cent), diphtheria (3 per cent), as well as those with a blood pressure over 140/90 mm. Hg (4 per cent) or who were 25 per cent or more above the average weight for their height according to a standard-build table (1 per cent). Heart murmurs (2 per cent) were also noted. These were believed to be innocent, since persons with organic murmurs were not accepted for flying training.

The initial electrocardiograms of most of those taking part in the study were normal. A special effort was made, however, to locate the few whose original records were known to have been abnormal. The majority of the subjects live in Canada but many have taken up residence in the United Kingdom, the United States and elsewhere. Approximately forty per cent are still flying, but with the passage of time the number actively so engaged is decreasing.

Original electrocardiograms, clinical reports, and home addresses were obtained from the R.C.A.F. for service personnel and from the Department of Transport for civilian pilots.* Establishing contact with living members of the 3 designated groups extended over a 2-year period. By June 1948, a total of 3,983 acceptable cases having been accumulated, the study population was sealed.

Contact is reestablished annually by means of a return postal card and examinations are authorized at 5-year intervals. The subject reports either to a designated physician in his area or to his own selected examiner. The required information for commercial pilots is obtained from the Department of Transport. It is one thing to establish contact with an individual but another to have the completed examination form and electrocardiogram filed in this laboratory. Mortality investigations require only a knowledge of whether those participating are alive or dead but to document the effects of time and disease upon the electrocardiograms of a maturing population, both serial electrocardiograms and complete clinical histories covering the observation period are essential. While most authorized examinations are completed promptly, much time is required to obtain reports on a few.

When the results of an examination suggest the presence of cardiovascular disease, the individual is referred to his own doctor and the details of any reported illness are obtained from attending physicians and hospitals. Without exception clinical information and copies of electrocardiograms recorded in connection with health studies or during the course of clinical illness have been made available. In the event of death an official death certificate, details of the terminal illness, and autopsy reports are procured.

*Records are maintained on an additional 78 healthy pilots with abnormal electrocardiograms who do not qualify for the study. They include persons who are known to be alive but who for a variety of reasons have not been examined since they left the service, as well as younger pilots examined for the Department of Transport whose abnormal electrocardiograms were discovered since 1948.

Table 1

Age Distribution on Entry and at Last Examination

Age Groups	On Entry Number	%	Last Examination Number	%
15-19	236	5.9		
20-29	2,797	70.2	274	6.9
30-39	756	19.0	2,468	61.9
40-49	164	4.1	1,035	26.0
50-59	30	0.8	158	4.0
60 plus			48	1.2
Total	3,983	100.0	3,983	100.0

Table 2

Exposure and Deaths during Follow-up Period

Years in Study	Number of Cases	Life Years	Deaths
5	81	405	9
6	117	702	18
7	145	1,015	9
8	218	1,744	11
9	327	2,943	13
10	571	5,710	6
11	512	5,632	5
12	506	6,072	4
13	190	2,470	1
14	281	3,934	3
15	247	3,705	1
16	477	7,632	1
17	311	5,287	2
Total	3,983	47,251	83

Results

Age Distribution

The age distribution of the population at entry and at the time of the last examination is shown in table 1.

The mean ages were 27.0 years at entry and 37.6 years at the time of the last examination. At the beginning of the study there were only 194 (4.9 per cent) aged 40 or over in contrast to 1,241 (31.2 per cent) at the last examination. However, of the 1,035 in the fifth decade 72.5 per cent were between 40 and 44 years.

Exposure and Deaths

Based upon the year of last contact, table 2 shows the population distributed according to the number of years of follow-up.

The population has been under observation for a total of 47,251 life years and 78 per cent have been followed up for 10 or more years with a mean exposure of 11.9 years. Contact has been lost (December 2, 1958) with 2 individuals.

During this period there were 83 known deaths. Of these, 53 or 64 per cent were due to aircraft accidents, 6 to other accidents, and 3 to suicide. Malignant disease accounted for 8 deaths, myocardial disease 7, poliomyelitis 3, and 1 each of pancreatitis, aplastic anemia, and primary pneumococcal pericarditis.

Myocardial Disease Diagnosed During the Period of Observation

Clinical heart disease, excluding uncomplicated hypertensive heart disease, was diagnosed in 35 people during the period of observation. This figure includes 2 cases of acute pericarditis and 1 of acute rheumatic fever. The 32 remaining cases are grouped to show the evidence upon which the presence of myocardial disease was assumed to be present.

Pathologic Q waves developed in the electrocardiograms of 22 people whose previous tracings showed normal QRS deflections; only 2 of these were without symptoms. There were 3 deaths; in the 2 who came to necropsy coronary artery disease with myocardial infarction was confirmed.

Acute chest pain diagnosed clinically as myocardial infarction occurred in 4 other subjects. T-wave changes, with or without a shift in RS-T segments, coincided with the illness but no Q waves appeared. Of these, 1 subject died but no autopsy was performed.

There were 2 sudden deaths following an episode of acute chest pain. Autopsy on one of these subjects confirmed the presence of coronary artery disease with acute myocardial infarction.

Two subjects developed classical angina of effort, presumably due to coronary artery disease, while another at autopsy was found to have coronary atherosclerosis with diffuse myocardial fibrosis. There was 1 example of extensive pericardial calcification, presumably with scarring of the subepicardial myocar

Table 3

Classification of Electrocardiograms on Entry and at Last Examination

Classification of Electrocardiograms		Entry		Last Examination					
				Normal		Abnormal			
						Questionable		Definite	
		Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
Normal		3,832	96	3,747	98	41	1	44	1
Abnormal	Questionable	109	3	38	35	68	62	3	3
	Definite	42	1	6	14	—		36	86
Total		3,983		3,791	95	109	3	83	2

lium.[8] On the basis of electrocardiograms lone myocardial disease was suspected in thers, but so far no confirmatory clinical vidence has appeared.

Myocardial disease was recognized at a nean age of 48 years (range 32 to 67 years). The 32 cases were distributed by age groups as follows: 30 to 39, 4; 40 to 49, 12; 50 and over, 16. Of the 4 cases in the fourth decade 2 had frank myocardial infarction, 1 angina pectoris, and 1 pericardial calcification.

Classification of Electrocardiograms

The electrocardiograms were placed in 2 broad classes: normal and abnormal, on the basis of changes in form, rhythm, and conduction, which are usually considered to be outside the accepted range of normal. While such a classification is subject to personal bias, all records were interpreted by one of the authors (F.A.L.M.) and every attempt was made to classify the observed abnormalities in a consistent manner.

Electrocardiograms received in this laboratory are recorded by many different physicians and institutions. There is no effective control over the number of leads submitted and, particularly in earlier records, the 3 limb leads alone or with a single precordial lead was the rule. The majority of recent records include the 12 standard leads. Accepted techniques are usually followed but some tracings are of doubtful quality, since at times they were taken on obviously faulty instruments. When the electrocardiogram is of poor quality, another one is requested but in borderline cases the probable significance of a recorded variant rests upon the judgment of the interpreter. The form of the electrocardiogram of a healthy person remains remarkably constant; particularly is this so of the limb leads, which are technically the least subject to variation. However T waves are unstable and, when a decrease in amplitude is first observed, it is difficult to know whether it is a normal fluctuation or a change that is to remain or become more marked with time. For this reason abnormal electrocardiograms were classified as *questionable* when the changes were possibly due to technical error or to a variation within the normal range, or *definite* when there was no reasonable doubt that a true alteration in the electrical activity of the heart muscle or conducting pathways had occurred. The distribution of normal and abnormal electrocardiograms on entry and at the time of the last examination is shown in table 3.

On entry, the electrocardiograms of 3,832 persons were normal. At the last examination 41 of these were questionable, 44 were abnormal, and of the 3,747 whose records were still normal when last examined 44 showed transient changes only during the intervening years. Of these 3,832 persons 27 (0.7 per cent) developed clinical evidence of myocardial disease.

The electrocardiograms of 151 individuals were abnormal on entry, 109 were questionable, and 42 were definitely abnormal. At the last examination 35 per cent of those classified as questionable were normal, 62 per cent were still questionable, and 3 per cent had become definitely abnormal. Of the 42 classified as definitely abnormal on entry 14 per cent returned to normal and the remaining 36 were unchanged. Five (3.3 per cent) of this group

Table 4

Minor Variants Observed in Electrocardiograms during Follow-up Period

Minor Variants	Total	
	Number	Per Cent
P-wave changes	6	2
Low amplitude QRS	14	4
Premature beats	100	28
Sinus bradycardia	184	52
Sinus tachycardia	22	6
Sinus arrest	2	1
Shifting pacemaker	5	1
Nodal rhythm (Const.)	4	1
Nodal rhythm (Parox.)	19	5
Total	356	100

of 151 developed myocardial disease. There was a total of 280 individuals or 7 per cent of the population who, on at least one occasion, showed an abnormal electrocardiogram.

Certain electrocardiographic abnormalities were characteristically unstable, appearing and disappearing from record to record in an unpredictable manner. This applied particularly to partial heart block,[7] paroxysmal tachycardia, shifts in RS-T level, and primary T-wave changes. In some instances the abnormality was due to artifact, which could be identified only when further records became available for comparison. With few exceptions QRS voltage changes, pathologic Q waves, complete heart block, Wolff-Parkinson-White configuration, and bundle-branch block remained constant once they appeared.

Major and Minor Variants

Changes that cause the electrocardiogram to be placed in the abnormal group are referred to as major variants, whereas those thought to be of less importance are classified as minor variants. This division of unusual electrocardiographic components, while arbitrary, provides a useful method of handling large numbers of variants and does not preclude the reclassification of any one item at a later date, should experience so indicate.

Minor Electrocardiographic Variants

In table 4 are listed the minor electrocardiographic variants observed over the follow-up period. Sinus tachycardia and bradycardia are included only when they occurred on 2 or more occasions.

The prognostic significance of these variants is unknown. Do people with slow heart rates live longer than those with persistently fast heart rates? Are individuals who frequently exhibit premature beats more likely to develop major arrhythmias? The evidence to date offers no answer to these questions.

Major Electrocardiographic Variants

The procedure followed in classifying abnormal components representing ventricular activity was to code the dominant QRS variant only and omit RS-T and T-wave changes secondary to it, variations in the latter being coded only when they occurred as primary events. When 2 variants appeared independently, each was listed.

In table 5 appear the major electrocardiographic variants that occurred alone or in association with clinical heart disease, showing for each class the number affected, the mean age, exposure, cardiovascular morbidity, and deaths.

The small numbers in many of the classes and the relatively few cases of myocardial disease caution against the use at this time of statistical tests of significance.

Partial heart block, the Wolff-Parkinson-White configuration, and right bundle-branch block, 3 of the more commonly observed variants, occurred in people whose mean age was under 30 when the abnormality was first recorded. In most instances it was present in their initial records. The 5 deaths in these 3 classes were due to accident. With the exception of 1 case of partial heart block, which was present for many years before and after myocardial infarction, the subjects exhibiting these variants have remained in good health.

High QRS voltage, RS-T depression, and left bundle-branch block were first observed at mean ages over 40 years. Seven of the 9 subjects with high QRS voltage had hypertension, and 3 of these developed coronary artery disease. These classes are too small to permit any reliable evaluation of their significance.

Table 5

Major Variants Observed in Electrocardiograms during Follow-up Period

Variant	Number	Mean Age Entry	Mean Age Variant First Recorded	Mean Exposure (Yr.) Total	Mean Exposure (Yr.) Variant	Myocardial Disease	Deaths
Apparent good health							
Low QRS voltage	4	31.7	36.0	10.3	6.0	1	1 (1)*
High QRS voltage	9	34.5	42.3	11.8	4.0	3	0
RS-T depression	3	31.7	40.4	11.0	2.3	0	0
Primary T wave changes	114	29.1	33.7	11.9	7.3	7	4 (2)
RS-T & T wave changes	3	26.0	30.7	12.7	8.0	1	0
Atrial tachycardia	8	32.6	36.7	13.9	9.8	0	0
Partial A-V block	76	28.1	29.6	13.1	11.6	1	3
Complete heart block	4	30.5	32.8	10.5	8.2	0	0
Wolff-Parkinson-White	13	25.9	28.2	10.3	8.0	0	0
Right bundle-branch block	30	27.2	28.1	10.9	10.0	0	2
Left bundle-branch block	3	40.7	42.3	11.6	10.0	0	0
Intraventricular block—others	2	24.5	24.5	13.5	13.5	0	0
Coincident with Myocardial Disease							
Pathologic Q waves	22	38.1	47.6	13.3	3.8	22	3 (3)
T-Wave changes with or without RS-T depression	4	48.5	57.8	13.5	4.2	4	1 (1)
Total Variants	295	29.8	33.6	12.2	8.4	39	14 (7)
More than 1 variant	15					8	1 (1)
Subjects with:							
Abnormal ECG[5]	280					31	13 (6)
Normal ECG[5]	3,703					1	70 (1)
Total population	3,983	27.0		11.9		32	83 (7)

*Deaths from myocardial disease.

The atrial tachycardias include 3 cases each of paroxysmal atrial tachycardia and atrial fibrillation, 1 chronic atrial fibrillation, and 1 unidentified paroxysmal tachycardia. Three of the 4 examples of complete heart block are believed to be of congenital origin.[9]

Those exhibiting primary T-wave changes are a heterogeneous group. In specific instances the changes were due to intercurrent infection, the upright position of the subject when the record was taken, or the postprandial response, while in others they were clearly related to myocardial ischemia, the evidence for which is presented in Part II. The mean age at which T-wave changes were recorded was 33.7 years. Approximately 75 per cent when last examined were under the age of 40, which parallels the age distribution of the total population.

In 26 instances abnormal electrocardiograms occurred in conjunction with clinical illness. Pathologic Q waves, accepted as positive evidence of transmural myocardial infarction, developed in the electrocardiograms of 22 subjects at a mean age of 47.6 years (range 36 to 57 years). Initial infarction occurred in the anterior myocardium in 13 instances and in the posterior in 9. In 4 of those with anterior lesions a second infarction occurred in the posterior wall.

In 4 cases presenting the clinical picture of myocardial infarction T-wave changes with RS-T displacement but without the appearance of Q waves were observed. These changes, which lasted for weeks or months before reverting in part or completely to their original form, were accepted as evidence of subendocardial infarction. These subjects entered the study at a mean age of 48.5 years with infarction occurring at 57.8 years.

Discussion

It is not possible as yet to establish the value of the routine electrocardiogram as an aid to the diagnosis of myocardial disease in this population, of which 69 per cent are still under the age of 40 years. Data pertinent to the objectives of this study may, however, be expected to accumulate rapidly in the years immediately ahead.

In this highly selected group myocardial disease has developed in only 1 individual whose original electrocardiogram was abnormal under the age of 30. Partial heart block, the Wolff-Parkinson-White configuration, and right bundle-branch block at the observed ages have not so far been forerunners of myocardial disease. It is not known whether this will hold when those affected reach the ages at which the clinical picture of myocardial disease makes its appearance. Some of the subjects whose electrocardiograms exhibited high QRS voltage, low QRS voltage, or T-wave variations did develop myocardial disease. Eventually it may be shown that such changes in the electrocardiogram of an apparently healthy person are evidence of subclinical disease but they do not necessarily indicate that acute illness is imminent, as in many cases their presence was found to be compatible with years of symptom-free living.

Some of the observed abnormalities were due to artifact. Much of this difficulty could have been avoided by observing accepted technics and incorporating a constant standardization signal of 0.20-second duration in all leads. This precaution is particularly important when electrocardiograms from different sources are submitted to a central laboratory for interpretation. To follow such a procedure, however, does not relieve the operator himself from the responsibility of maintaining a constant watch on the sensitivity and response characteristics of his instrument. All too frequently the electrocardiograms submitted over a period of months, even years, from the same source showed clearly that the electrocardiograph required servicing. This fact continued to escape the notice of the physician responsible for the quality of the records. Attention to these details would reduce the number of instances in which doubt is cast upon the soundness of the heart of an apparently healthy person.

Conclusions

A population of 3,983 apparently healthy people whose mean age at entry was 27.0 years was followed with periodic medical examinations and electrocardiograms for a period of 10.6 years. Based upon the date of last contact the mean exposure was 11.9 years. There were 83 deaths, of which 7 only were from myocardial disease. Thirty-two subjects developed clinical myocardial disease at a mean age of 48 years.

Of those who entered the study with abnormal electrocardiograms 3.3 per cent have so far developed myocardial disease in contrast with 0.7 per cent for those whose initial electrocardiograms were normal.

Two hundred and eighty subjects, 7 per cent of the population, on at least 1 occasion had an abnormal electrocardiogram.

Partial heart block, paroxysmal tachycardia, shifts in RS-T level and primary T-wave changes tended to occur intermittently, while QRS voltage changes, pathologic Q waves, complete heart block, Wolff-Parkinson-White configuration, and bundle-branch block usually remained constant once they appeared.

At the observed ages and durations the subjects whose electrocardiograms exhibited partial heart block, Wolff-Parkinson-White configuration, and right bundle-branch block have remained, with 1 exception, in apparent good health.

Low QRS voltage, high QRS voltage, and primary T-wave changes with or without a shift in the RS-T segments were the only abnormal electrocardiographic components that preceded the onset of myocardial disease but many showing these and other abnormalities in the electrocardiogram have not so far developed clinical evidence of disease.

More attention to technical details and standardization requirements would reduce the number of abnormal electrocardiograms in apparently healthy people.

This long-term follow-up study, the object of which is to determine the clinical significance of abnormal electrocardiograms in apparently healthy people, has now a well-established baseline on a population of 3,983 persons. As the majority of those under investigation are approaching the age at which myocardial disease becomes clinically recognizable, the value of the study will increase in the years immediately ahead.

Acknowledgment

We wish to acknowledge the financial assistance of the National Research Council of Canada who supported this study in its early years and the Defence Research Board who have carried the burden since then. We are indebted to Mr. J. E. Morrison, F.S.A., for his friendly guidance in the preparation and programming of the material for this report and to Dr. A. H. Sellers, and Mr. W. A. Keltie, F.S.A., for their critical reviews of the manuscript. To Miss Joyce Neufeld, Warrant Officer R. Leathwood, R.C.A.F., and Mr. A. H. Beamish, who have been responsible for the follow-up system and the other procedures essential to the conduct of this study, go our sincere thanks.

Summario in Interlingua

Un population de 3.983 personas in apparentemente bon sanitate, de un etate initial medie de 27,0 annos, esseva tenite sub observation, con periodic examines medical e studios electrocardiographic, durante un periodo medie de 10,6 annos. Septanta-octo pro cento del gruppo total esseva sub observation durante periodos de plus que 10 annos (duration medie, 11,9 annos). Occurreva 83 mortes, incluse solmente 7 causate per morbo myocardial. Trenta-duo del subjectos disveloppava clinic morbo myocardial a un etate medie de 48 annos.

Inter le subjectos con anormalitates electrocardiographic al tempore de lor entrata in le studio, 3,3 pro cento ha disveloppate morbo myocardial usque iste tempore. Le correspondente procentage pro le subjectos con normal electrocardiogrammas initial es 0,7.

Duo centos octanta subjectos, i.e. 7 pro cento del population total, habeva un electrocardiogramma anormal a al minus un occasion.

Partial bloco cardiac, tachycardia paroxysmal, displiciamentos del nivello RS-T, e primari alterationes de unda T tendeva a occurrer intermittentemente, durante que alterationes del voltage de QRS, undas Q pathologic, configuration Wolff-Parkinson-White, e bloco de branca remaneva constante in le majoritate de casos in que illos se manifestava.

Non respecto al subjectos in qui le electrocardiogramma ha exhibite partial bloco cardiac, configuration Wolff-Parkinson-White, o bloco de branca dextere, on pote dicer que intra le limites del etates representate e del durationes de observationes illes omnes, con 1 exception, ha remanite in stato de apparentemente bon sanitate.

Basse voltage de QRS, alte voltage de QRS, e primari alterationes de unda T con o sin displaciamentos in le segmento RS-T esseva le sol anormalitates electrocardiographic que precedeva le declaraton de morbo myocardial, sed in multe casos in que iste e altere anormalitates del electrocardiogramma esseva notate, nulle signo clinic del morbo ha devenite manifeste usque a iste tempore.

Un plus meticulose attention prestate al detalios technic e al requirimentos de standardisation reducerea le numero del electrocardiogrammas anormal in personas de apparentemente normal sanitate.

Iste studio de controlo a longe vista, que ha como su objectivo determinar le signification clinic de electrocardiogrammas anormal in personas de apparentemente normal sanitate, possede nunc un firme base in un population de 3.983 subjectos. Viste que le majoritate del individuos includite in le investigation procha le etate al qual morbo myocardial deveni clinicamente recognoscibile, le valor del studio va crescer in le curso del annos immediatemente ante nos.

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Abnormal Electrocardiograms in Apparently Healthy People

II. The Electrocardiogram in the Diagnosis of Subclinical Myocardial Disease Serial Records of 32 People

By F. A. L. MATHEWSON, M.D., AND G. S. VARNAM, M.D.

ROUTINE electrocardiograms and clinical examinations were recorded over a 10-year period on a selected population of 3,983 subjects who were in good health when first examined at a mean age of 27 years. The general plan of the investigation is outlined in Part I.[1] During the follow-up period 32 men developed clinically recognizable myocardial disease; in most instances coronary artery disease was the underlying cause. It is the purpose of this report, by relating the serial electrocardiograms of these people to the sequence of clinical events, to show the extent to which the routine electrocardiogram contributed to the diagnosis of myocardial disease and to the recognition of those specific abnormalities in the electrocardiogram which indicate the presence of subclinical disease.

Apart from the electrocardiograms of 3 subjects which were abnormal on entry, the elapsed time between the last normal routine record and recognition of clinical disease varied from a few months to 7 years. In 23 instances it was 4 or less years.

Results

Routine electrocardiograms in 17 of the 32 subjects were not of diagnostic value in predicting the presence of coronary heart disease and with one exception, were normal up to the time of the clinical event. Case no. 475-400 exhibited intermittent partial heart block for many years before and after 2 distinct myocardial infarctions. Since the block was unaffected by these illnesses making any causal relationship between them remote, this case was included in the nondiagnostic group. Each of these subjects developed an acute clinical episode: 14 transmural infarctions, 2 subendocardial infarctions, and 1 acute chest pain preceding sudden death. The interval between the last normal record and the clinical event averaged 3.2 years and was 5 or less years in 15 instances. The following example illustrates the brief period which may elapse between a normal routine record and the onset of myocardial infarction.

Case no. 874-300 entered the study at age 39. Routine electrocardiograms on March 12, 1945, and on January 5, 1951, (fig. 1) were identically normal. On March 23, 1951, 11 weeks after his last normal record, he developed an acute posterior myocardial infarction. Electrocardiographic evidence of this illness is seen in the records of March 31, 1951, and April 29, 1957.

In the other 15 subjects, representing 47 per cent of those affected, the routine electrocardiogram was clearly of diagnostic value. These cases are arranged in 3 groups. In group 1, 3 subjects whose electrocardiograms were abnormal on entry are considered separately as each presents some feature of particular interest. Group 2 includes 5 subjects in whom the routine electrocardiogram identified unrecognized transmural infarction. Group 3 comprises 7 examples of primary T-wave changes occurring in asymptomatic subjects who later developed clinically recognizable

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This study is supported by Grant No. 8810-02 of the Defence Research Board, Department of National Defence, Ottawa, Canada.

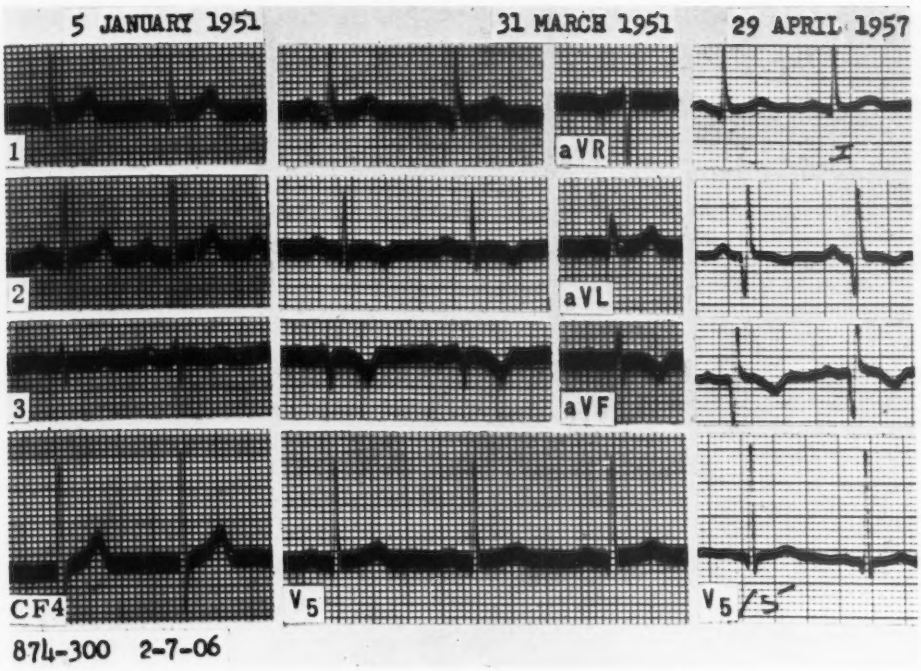

Figure 1
Electrocardiogram, case no. 874-300.

coronary artery disease. In both groups 2 and 3 the elapsed time between the last normal electrocardiogram and the first recorded change was 3.6 years.

Group 1

Case no. 783-000 first came under observation in 1940 at age 46. His initial electrocardiogram showing low QRS voltage with secondary T-wave changes was identical with that dated August 8, 1944 (fig. 2). He was an active healthy individual with normal findings on examination. His heart size by x-ray was normal. On repeated inquiry no clinical event could be identified to account for his abnormal electrocardiogram. He was retired in the fall of 1945 and apart from fatigue remained in good health until 1952 when at age 58, 12 years after his abnormal electrocardiogram was discovered, he became short of breath for the first time. Progressive left ventricular failure and cardiac enlargement developed over the next 4 years, with death occurring at age 62. During the whole period of observation up to the terminal illness his electrocardiograms remained identically abnormal. At necropsy his heart weighed 600 Gm. There was marked disproportion between the 2 main coronary arteries; the small right artery, which was practically free from atheroma, terminated abruptly over the posterior and lateral aspects of the right ventricle, while the large left vessel, which supplied the rest of the myocardium, showed marked atheroma in both the circumflex and descending branches with a recent occlusion in the latter. There were no visible anastomoses between the right and left coronary arteries. The aortic orifice of the left coronary artery was very large, whereas that of the right was pin-point in size. There was a diffuse increase in fibrous tissue throughout the myocardium but no definite area of old infarction could be demonstrated.

It appears likely that the electrocardiographic changes were due to long-standing ischemic myocardial fibrosis in a heart exhibiting an unusual distribution of coronary vessels with atherosclerosis restricted to the disproportionately large left coronary artery. While the coronary arteries were not perfused, there were no visible anastomoses among the branches.

Case no. 385-610 was first examined on May 14, 1941, as a student pilot aged 25. He was apparently in good health and general examination was normal except for a faint apical systolic murmur

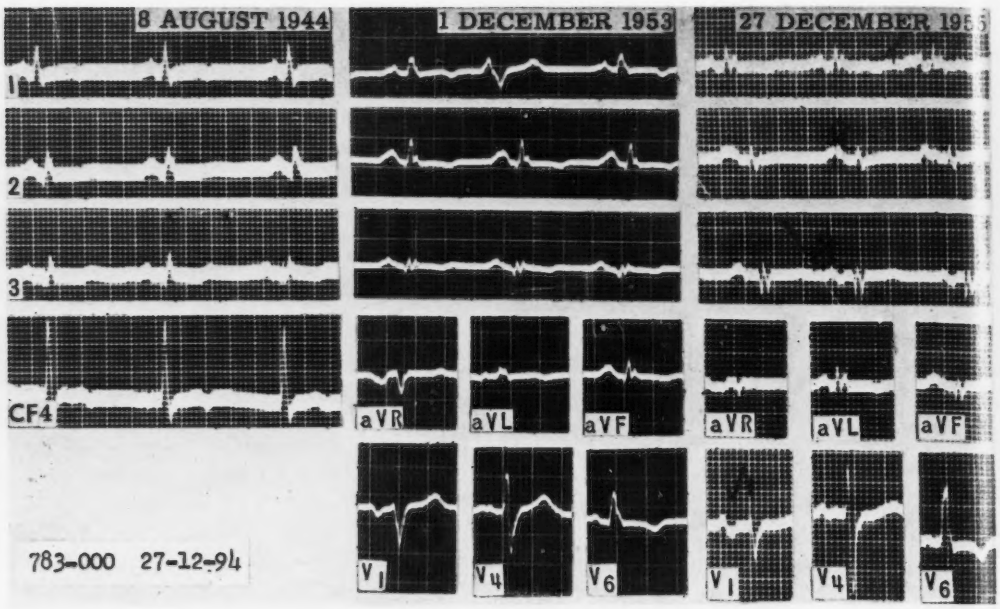

Figure 2

Electrocardiogram, case no. 783-000.

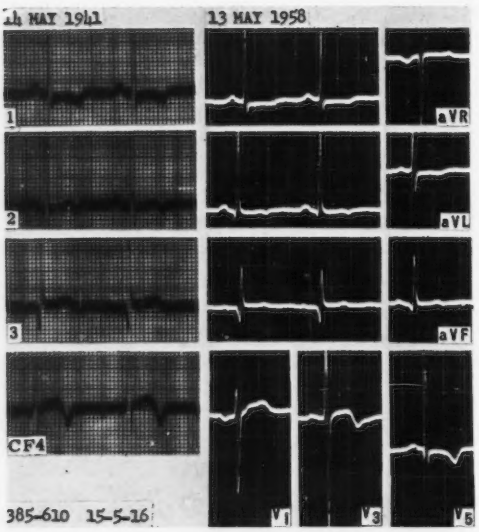

Figure 3

Electrocardiogram, case no. 385-610.

and a cardiothoracic ratio in the enlistment chest film of 14.3/28 cm. His initial and most recent electrocardiograms both show high QRS voltage and secondary RS-T and T-wave changes (fig. 3). After review by a medical board he was permitted to complete pilot training and served in this capacity until retired from active service in November 1945. Substernal tightness on exertion first appeared in 1953 and by 1958 the classical picture of angina pectoris was established. In 1956 the cardiothoracic ratio by fluoroscope measured 14.3/28 cm. His blood pressure was normal on all occasions. A pulmonary systolic murmur heard in 1958 was the only murmur reported since 1941. He continues to be actively employed.

The form of his electrocardiograms, which suggests left ventricular hypertrophy, and his heart size by x-ray remained remarkably constant over a period of 17 years. Because of the age at which the abnormality was first discovered and the absence of significant clinical history at that time, it is unlikely that the primary pathologic process is coronary atherosclerosis. An anomalous coronary circulation with atherosclerosis impeding blood flow as a recent complication would appear a more likely explanation.

Case no. 96-460 entered the study at age 32. Nine years later it was established that he had marked pericardial calcification. His electrocardiograms throughout the period of observation showed widely distributed RS-T depression and inverted T waves with a gradual increase in QRS voltage. The clinical details are given in case no. 2

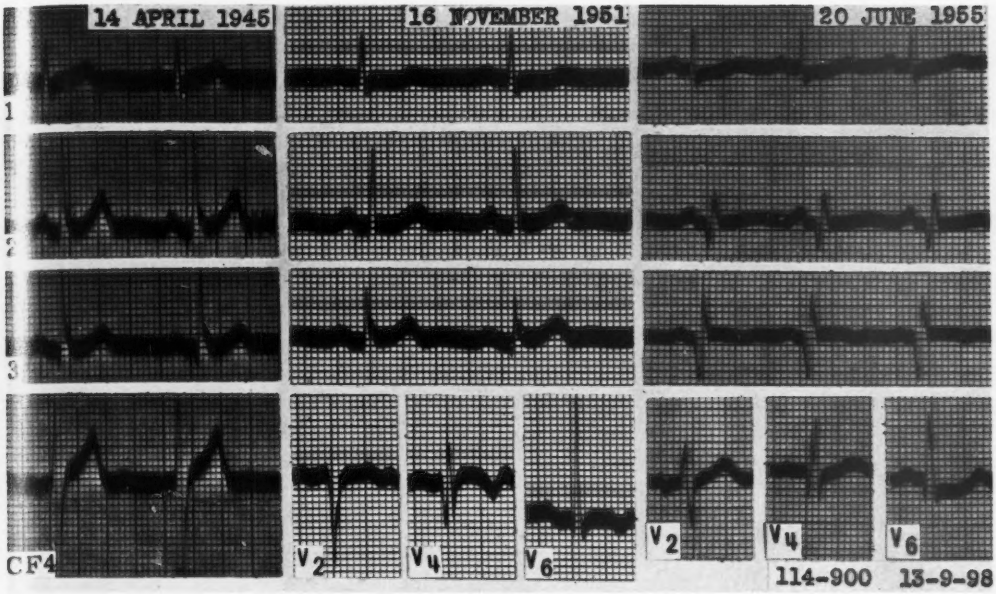

Figure 4

Electrocardiogram, case no. 114-900.

of a previous publication.[2] This case has been included as one of myocardial disease on the assumption that scarring of the epicardial surface of the myocardium disturbed the normal process of repolarization.

Comment

The routine electrocardiograms of these 3 subjects were grossly abnormal on entry and the observed changes remained constant in all subsequent records. They correctly identified the presence of subclinical myocardial disease while the subjects were apparently in good health.

Group 2

Pathologic Q waves indicating transmural infarction occurred in 5 subjects who were either asymptomatic or had obscure symptoms not recognized as cardiac in origin. The Q waves were discovered at a mean age of 4 years, the range being 44 to 53 years. There were 3 posterior infarctions and 2 anterior ones. In 2 instances epigastric distress was the presenting symptom, in 1 chest pain was attributed to a fractured rib, and 2 were entirely asymptomatic. An example of each type is given.

Case no. 114-900 entered the study at age 47. His tracing on June 4, 1948, was identical with the initial record of April 14, 1945 (fig. 4). The next routine electrocardiogram taken on November 16, 1951, showed a low T-wave in lead I and an increase in QRS-T angle. A QS deflection was present in V_2 and V_3, a deep Q wave in V_4, and T-wave inversion in all chest leads; a clear picture of anteroseptal infarction, which had occurred at some time since the previous record. The story then developed that this man had chronic heartburn and had consulted his physician on January 25, 1951, because of increased postprandial distress relieved by baking soda. Gallbladder and upper gastrointestinal x-ray examinations were normal. An electrocardiogram was not recorded. On June 20, 1955, a second infarct occurred; this time it was posterior.

Case no. 628-500 was 38 when first examined. Electrocardiograms taken on February 20, 1945, and July 8, 1948, were identically normal (fig. 5). His next routine tracing dated November 7, 1951, showed for the first time Q waves with associated T-wave changes in leads II and III characteristic of posterior infarction. He was referred to a qualified internist who developed the story that on August 30, 1951, he had strained his shoulders catching a 100-pound bag of flour that slipped during the unloading of an aircraft. The following day substernal pain developed, which was

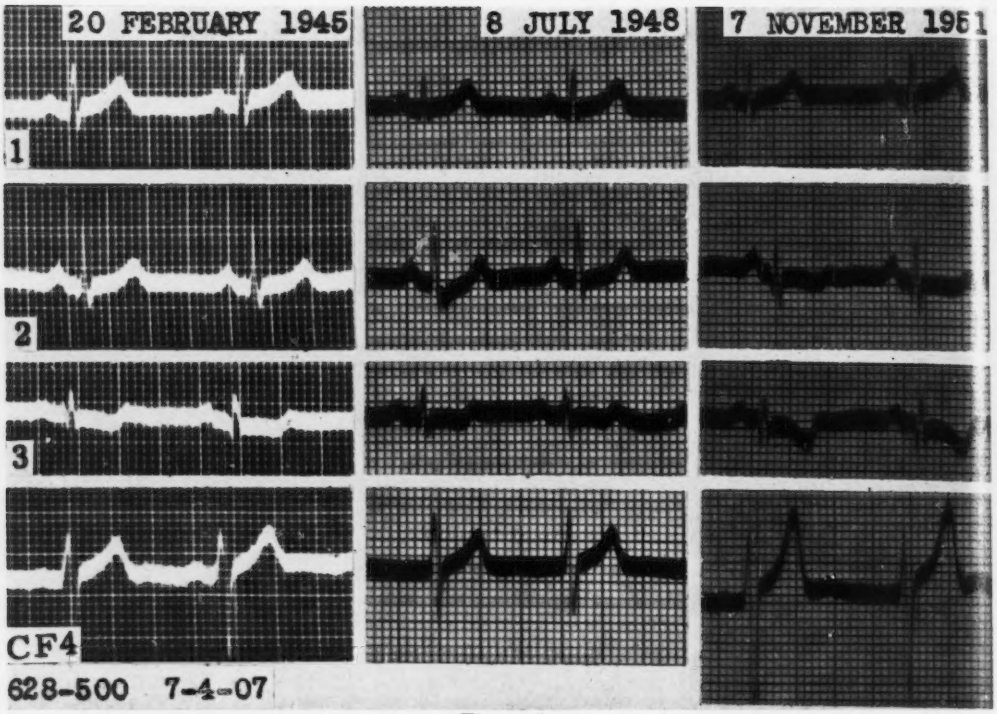

Figure 5

Electrocardiogram, case no. 628-500.

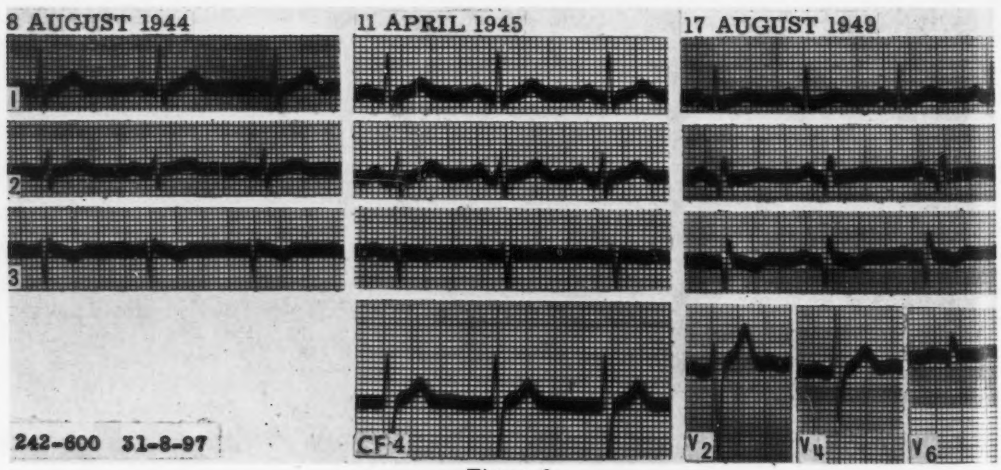

Figure 6

Electrocardiogram, case no. 242-600.

thought to be due to a cracked rib seen in the chest x-ray film. Since then he has had chest pain consistently on walking. An electrocardiogram following exertion showed acute depression of the RS-T segments characteristic of myocardial ischemia.

Case no. 242-600 who entered the study at age 47 had normal electrocardiograms on August 8, 1944, and April 11, 1945 (fig. 6). The next routine tracing dated August 17, 1949, showed well-developed Q waves in leads II and III although no significant clinical event could be identified.

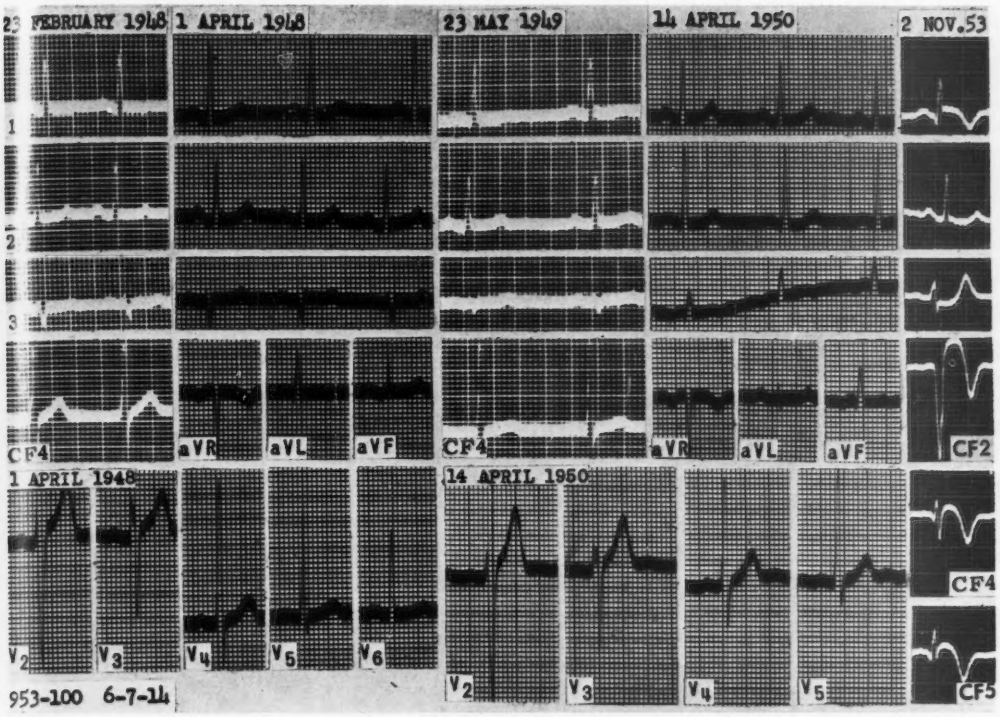

Figure 7

Electrocardiogram, case no. 953-100.

One month later a transient hemiplegia occurred.

The possibility of a cerebral embolus from a mural thrombus was considered but Paton's[3] recent observation that myocardial infarction and cerebrovascular accidents not uncommonly occur coincidentally perhaps offers a more likely explanation.

Comment

In view of the few cases of coronary artery disease that have developed so far in this study, it is surprising that 5 of them failed to be recognized clinically. Myocardial infarction escapes identification when there is failure to elicit pertinent information, when the event has been painless, or when the presenting symptoms are attributed to some other cause. The frequency of painless infarction in reported series depends upon the selection of cases and whether or not persons with a low pain threshold are included. Cases being limited to those who gave reliable histories, silent infarction was observed by Roseman[4] in 2.3 per cent of 220 cases of proved infarction from the files of the Boston City Hospital. It is not suggested that this figure reflects the incidence of this condition in the general population, since people with silent infarction would not usually enter hospital unless they developed heart failure or a major arrhythmia. A clinicopathologic study by Johnson et al.[5] based upon 1,267 necropsies performed at the Mayo Clinic for the years 1953 and 1954 showed that approximately 50 per cent of 113 healed infarctions had not been recognized clinically. Periodic electrocardiograms, which are taken according to a specified time schedule or form part of a general health examination without reference to a patient's symptoms, may be expected to identify infarctions that otherwise would go unrecognized.

Group 3

The electrocardiograms of the 7 subjects in this group developed primary T-wave changes

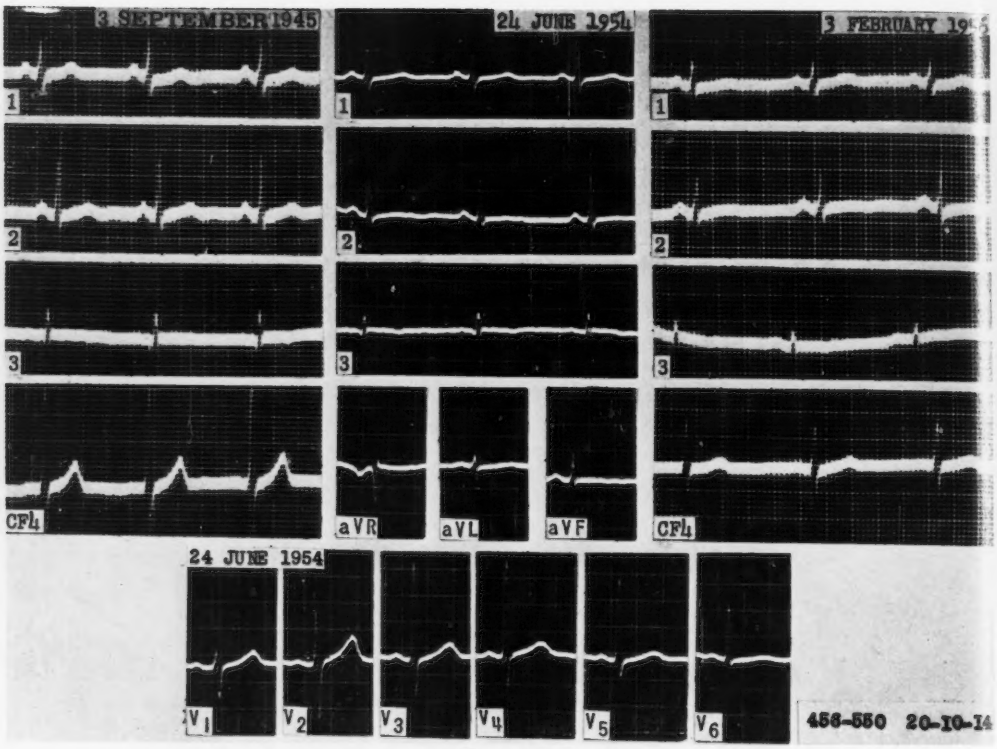

Figure 8

Electrocardiogram, case no. 456-550.

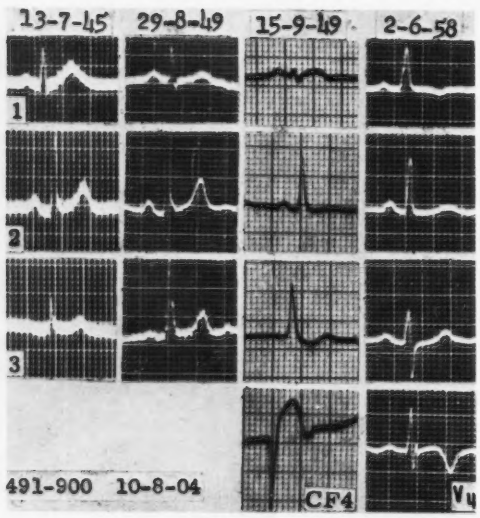

Figure 9

Electrocardiogram, case no. 491-900.

while they were still in good health, preceding by a few weeks to 6 years (mean 4 years) the onset of clinically recognizable coronary artery disease. These T-wave changes occurred at a mean age of 46 years (range 34 to 61 years) followed by the clinical event at a mean age of 50 years (range 39 to 67 years). There were 4 transmural infarctions, 2 subendocardial infarctions, and 1 classical case of angina pectoris. The following examples illustrate some of the characteristics of primary T-wave changes associated with subclinical coronary artery disease.

Case no. 953-100 entered the study at age 3[illegible]. He was of normal build and his blood pressure was 132/88 mm. Hg. His initial electrocardiogram dated January 15, 1945, was normal and identical with that of April 1, 1948 (fig. 7). On February 2[illegible], 1948, (blood pressure 140/90) primary T-wave changes were observed for the first time while th[illegible]

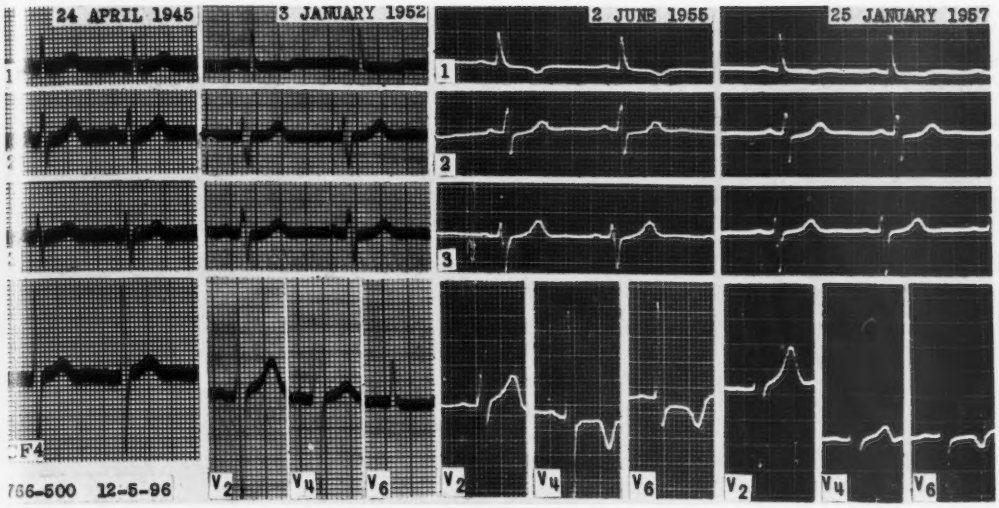

Figure 10

Electrocardiogram, case no. 766-500.

repeat tracing 2 months later was normal. Similar changes were observed again on May 23, 1949, (blood pressure 145/90) while on April 14, 1950, the record was again normal (blood pressure 150/90). By August 1951 he had gained 18 pounds and his blood pressure was 160/104 mm. Hg. On November 2, 1953, at the age of 39 an acute anterior myocardial infarction occurred. Recovery was uneventful. T-wave variations appeared intermittently over a period of 5 years before infarction took place.

Case no. 456-550 entered the study on September 3, 1945. His initial electrocardiogram (fig. 8) and that of July 25, 1950, were identically normal. The record of June 24, 1954, showed for the first time the T-waves to be flat in lead II and inverted in lead III. Similar changes were again present on February 3, 1956. He was asymptomatic, and clinical examinations were entirely normal throughout the period of observation. Death occurred suddenly on August 14, 1957, at the age of 43. Necropsy showed coronary atheromatous changes with a thrombus occluding the right coronary artery. The posterior wall of the left ventricle was infarcted, which corresponded with the area of myocardium indicated by the earlier T-wave changes. Here the primary T-wave changes apparently remained constant once they appeared.

Case no. 491-900 a 41-year-old flying instructor, was examined in connection with this study on July 13, 1945 (fig. 9). He was seen next on August 29, 1949. He had no complaints and normal findings were reported on examination. On September 15, 1949, 17 days later, he developed an acute anterior myocardial infarction.

This event might have been anticipated had there been time to compare his initial tracing with that of August 29, in which a reciprocal shift in the amplitude of the T-waves in leads I and III was clearly evident.

Case no. 766-500 entered the study at the age of 47. His electrocardiogram on November 24, 1943, was identical with that of April 24, 1945 (fig. 10) and his blood pressure on these occasions was reported to be 134/93 and 124/84 mm. Hg. On April 5, 1950, (blood pressure 148/92) his record showed a flat T-wave in lead I and this was also present on January 3, 1952. On June 2, 1955, he had his first episode of chest pain and 4 days later was admitted to hospital where he remained for 5 weeks with a diagnosis of myocardial infarction. His electrocardiogram showed a depressed RS-T segment in leads I and II with the T-wave in lead I definitely inverted. In V_4 to V_6 the RS-T segments were acutely depressed and the T-waves inverted. No pathologic Q waves appeared. These changes slowly regressed over the next 4 months. The follow-up tracing of June 25, 1957, is included to show that the T-waves returned to approximately what they were in 1952. The increased QRS voltage is attributed to left ventricular hypertrophy. His blood pressure in January 1957 was 164/110 mm. Hg.

The clinical history and serial electrocardiograms suggest that this hypertensive individual had a subendocardial infarction in June 1955. To

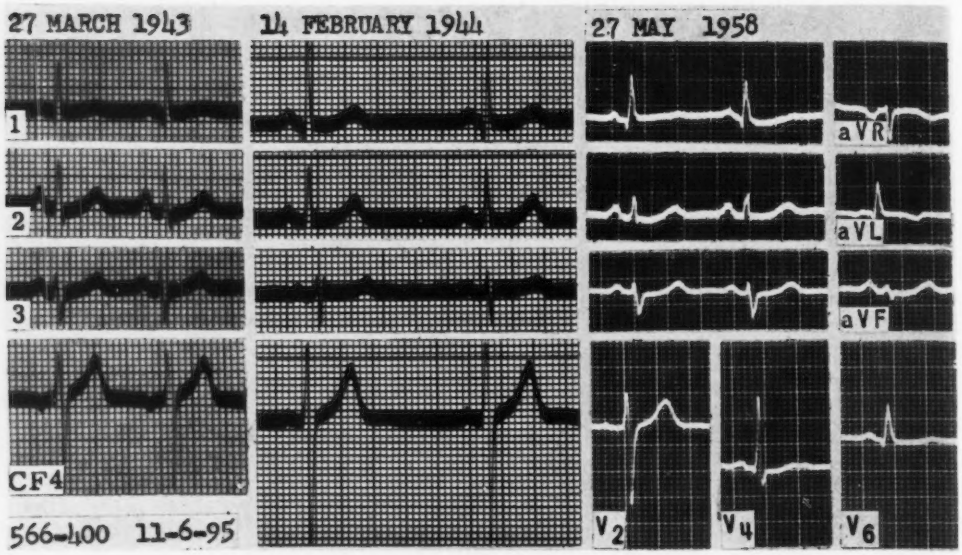

Figure 11

Electrocardiogram, case no. 566-400.

what extent hypertension contributed to the reciprocal shift in the amplitude of T_1 - T_3 first observed in 1950 is unknown.

Case no. 566-400 was in good health when first examined at age 48. In his initial tracing dated March 27, 1943, (fig. 11) the T-wave in lead I is low and $T_1 < T_3$, the QRS-T angle in the frontal plane being approximately 60°. His next routine tracing dated February 14, 1944, was normal. However, because of fatigue he was seen in consultation on March 28, 1944, at which time a repeat electrocardiogram again exhibited a flat T-wave in lead I. Subsequent annual electrocardiograms in 1945 and 1946 were normal. In 1946 because of intermittent chest pain not related to exertion an atypical form of angina pectoris was suspected. By 1950 he had classical retrosternal pain on exertion. Electrocardiograms taken at approximately 2-year intervals between 1950 and 1958 all showed flat T-wave changes, which had occurred intermittently in the earlier years.

Comment

In 3 of the 7 cases abnormal T-waves occurred as a transient event while in others they appeared to be fixed. In case no. 491-900 the reciprocal shift was related directly to the infarction, which occurred 17 days later. In none was associated chest pain reported. In the 4 cases of transmural infarction the earlier T-wave changes accurately identified the area of myocardium which eventually infarcted. Cases no. 953-100 and 456-550 are examples in point.

Dressler[6] in 1943 pointed out the importance of a reciprocal shift in the amplitude of the T waves in lead I and lead III as an indication of anterior wall infarction. While this reflects a change in the direction of the T-wave vector, which is recorded proportionately in the other frontal plane leads, it has proved to be useful and reliable evidence of abnormality, particularly where previous electrocardiograms are available for comparison. It is of less value in electrically vertical hearts in which all components of lead I tend to be minimal; even here when there are previous records for comparison it is useful. A vertically placed heart is no protection against anterior wall infarction.

A serious limitation to the use of primary T-wave changes as a sign of subclinical coronary artery disease is the fact that such changes also result from a variety of other causes. In this study the electrocardiograms of 114 subjects[1] have on at least 1 occasion

exhibited primary T-wave changes and of these, to date, only 7 have developed clinically recognizable coronary artery disease. Eventually it may be possible to identify characteristics that indicate their specific origin. In the meantime the presence of primary T-wave changes should raise the suspicion of coronary artery disease.

Conclusion

Changes in the electrocardiogram provided the first evidence of underlying myocardial disease in 15 or 47 per cent of 32 cases in which it was later possible to confirm the diagnosis.

In 5 subjects who were symptomless or who presented an atypical clinical picture the routine electrocardiogram established that unrecognized transmural myocardial infarction had occurred.

Evidence is presented to show that primary T-wave changes may indicate the presence of asymptomatic coronary artery disease. In the present state of our knowledge the practical value of this finding is limited.

Summario in Interlingua

Alterationes in le electrocardiogramma provideva le prime indication de un subjacente morbo myocardial in 15 inter 32 casos in le quales il esseva subsequentemente possibile confirmar le diagnose (47 pro cento).

In 5 subjectos qui esseva sin symptomas o exhibiva atypic aspectos clinic, le electrocardiogramma routinari establiva que un non-recognoscite infarcimento myocardial transmural habeva occurrite.

Es presentate datos que pare provar que primari alterationes del undas T indica le presentia de asymptomatic morbo de arteria coronari. Sub le conditiones del stato presente de nostre cognoscentias le valor practic de iste constatation es limitate.

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On Cardiac Murmurs

By AUSTIN FLINT, M.D.

Erroneous views respecting the significance of cardiac murmurs, and also respecting the indications for treatment in cases of organic disease of the heart, are still, to a greater or less extent, prevalent. I propose now to confine myself to the former, i.e., the significance of the murmurs. It is obvious that with the acquirement of means of ascertaining the existence of lesions at an early period, when, without these means, the lesions could not have been discovered, clinical experience had to take a new point of departure as regards prognosis. And experience has shown that lesions giving rise to cardiac murmurs by no means invariably denote danger or serious evils, and that they are not frequently innocuous.—*Am. J. M. Sc.* n.s. **44**:29, 1862.

Discordant Pulsus Alternans

By HENRY D. MCINTOSH, M.D.

ALTERNATION of the pulse pressure may occur simultaneously or independently in the systemic and pulmonary circulations.[1] When present in both systems mechanical alternans has been reported as being synchronous or concordant, i.e., the strong and weak pulses occurring in the 2 circulations during the same cardiac cycle. However, de Rabago and associates[2] postulated that alternation could occur discordantly. This assumption was based on an analysis of tracings obtained in sequence from a 2-year-old child with congenital heart disease. Unfortunately, pressures were not recorded simultaneously.

The purpose of this report is to demonstrate by simultaneously recorded pressure tracings that discordant mechanical alternans can indeed occur.

Case Report

H. M., a 60-year-old Negro farmer was first admitted to the Durham VA Hospital August 3, 1953, for exertional and paroxysmal nocturnal dyspnea, orthopnea, and easy fatigability of 7 months' duration. The physical examination revealed a blood pressure of 180/130 mm. Hg pulse of 100 per minute, and respirations of 40 per minute. Grade II hypertensive changes were present in the retinal vessels. Fine inspiratory rales were present throughout both lungs, except at the right base posteriorly, where there were dullness to percussion and diminished breath sounds. The heart was enlarged 2 cm. beyond the midclavicular line in the fifth intercostal space. Normal sinus rhythm was present. The aortic second sound was greater than the pulmonic. A grade-II systolic murmur was heard over the entire precordium, maximal along the left sternal border in the fourth intercostal space. The liver was enlarged 2 cm. below the right costal margin, but there was no edema.

From the Department of Medicine, The Duke Medical Center, Durham, N. C.

This investigation was supported (in part) by a Grant-in-Aid from the American Heart Association, a research grant from the Life Insurance Medical Research Fund, and research grants H-3343 and H-1217 from the National Heart Institute, U. S. Public Health Service.

The electrocardiogram demonstrated first-degree heart block and left bundle-branch block. The chest x-ray confirmed the impression of cardiomegaly with left ventricular enlargement, pulmonary congestion, and right pleural effusion. The arm-to-tongue circulation time (Decholin sodium) was 35 seconds. Other laboratory studies were not pertinent.

The patient responded to sodium restriction, bed rest, diuretics, and digitalization. He was discharged on the fifteenth hospital day essentially asymptomatic.

During the subsequent 27 months he was hospitalized 7 times with essentially the same history. It is of interest that during these admissions, contrary to the first, the patient was normotensive. The cardiomegaly increased. Both a protodiastolic and a presystolic gallop were intermittently present. Ankle edema was variable. Pulsus alternans was first reported July 1, 1954, 11 months after the first admission. No comment regarding this sign was made during the next 4 hospitalizations. It may well have been present but overlooked.

He was hospitalized for the last time on January 19, 1956, again with symptoms of congestive failure. The blood pressure was 124/86 mm. Hg and 4 to 10 mm. Hg of pulsus alternans was present. In view of the retinal changes and previous record of hypertension, the failure was thought to be due to hypertensive and arteriosclerotic cardiovascular disease.

Right heart catheterization was carried out and the patient was found to have alternans in the lesser circulation as well as in the systemic artery (fig. 1). The recorded alternans was always concordant except for 2 short intervals when the alternans was discordant (figs. 2 and 3). The hemodynamic findings (table 1) were compatible with left ventricular failure.

Discussion

Ferrer and associates[1] demonstrated that alternation of the pulse pressure in man can occur independently in the greater or lesser circulation without appearing in the other. Even when bilateral alternation exists, the phenomena may disappear in one circulation and persist in the other. These investigators stressed the relatively independent behavior of the 2 ventricles and their respective circ-

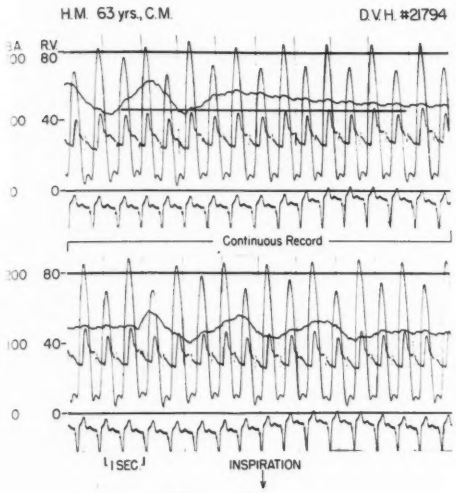

Figure 1

Simultaneous record demonstrating concordant pulsus alternans in both the right ventricle and brachial artery. The pneumotachygram indicates that respiration ceased in the upper tracing. The impulse during diastole in the brachial arterial tracing is an artifact produced by a constant infusion pump.

lations. In their experience, however, bilateral alternation was always concordant or synchronous.

De Rabago[2] reported alternation in both circulations in a 2-year-old child with an interatrial septal defect and anomalous left superior vena cava draining into the coronary sinus. Alternation of the "a" waves and the level of diastolic pressure in the atrial and venous pressure contours was present, as well as alternation of the arterial systolic pressure in both circulations. The diastolic pressure following the large "a" waves in the left jugular vein (draining by way of the anomalous left superior vena cava into the coronary sinus) was lower than that following the smaller "a" wave. The reverse relationship existed in the right atrium. This difference suggested to the authors that the alternans in the pulmonary circulation was discordant with that in the systemic circulation. They reasoned that the discordant alternans could be caused by "a surge of pressure which

Table 1

Hemodynamic Data

	Pressure mm. Hg		Oxygen Content vols. %	Oxygen % Saturation
Pulmonary "wedge"	(25)			
Pulmonary artery	75-85 / 40	(55)	10.6	52
Right ventricle	75-85 / 2	(40)		
Right atrium	(2)			
Brachial artery	100-110 / 70		20.8	97

Oxygen consumption 300 ml./min.

Cardiac output 3.16 L./min.; Cardiac index 1.77 L./min./M^2.

Mean circulation time (right ventricle=brachial artery) 39.5 sec.

swept around the circulatory tree during an interval equal to one-half the heart rate." Simultaneous tracings from the 2 circulations were not recorded, however, and the occurrence of discordant alternation in this case was based only on speculation.

In the present patient concordant pulsus alternans was observed intermittently throughout the entire catheterization (fig. 1). The alternation disappeared on occasions in one circulation while remaining in the other. On 2 occasions, however, the alternation in the brachial artery and right ventricle was discordant (figs. 2 and 3). The occurrence of the discordancy was not observed until after the procedure was completed; therefore, the phenomenon was not studied in detail.

That discordant pulsus alternans can occur, even if only for a few beats, is of considerable interest. No other simultaneously recorded tracings demonstrating this phenomenon have been found in the English literature. It would not have been detected in this patient had he not been asked to cease breathing periodically. If searched for, the phenomenon may not be uncommon.

Explanations of the mechanism of alternans have included a consideration of both myogenic and hemodynamic factors. Most investigators have considered variations in the

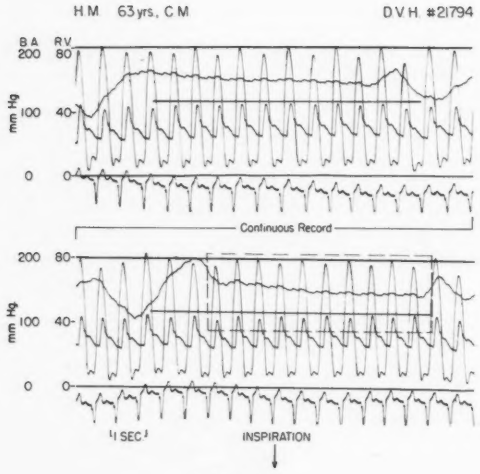

Figure 2

Simultaneous record demonstrating concordant pulsus alternans in both the right ventricle and brachial artery during the period of voluntary apnea in the upper tracing and discordant alternans during the apneic period in the lower tracing.

tension and volume of the ventricle at the end of the diastolic filling period to be of major importance in the propagation of the phenomena. There has not been general agreement, however, whether the changes in volume and tension arise from primary alternations in the vigor of muscle contraction or whether the latter are secondary to variations of inflow or resistance.

Wenckebach[3] in 1914 had suggested the importance of hemodynamic factors. With a scanty residual end-diastolic volume, the tension of the ventricle would be insufficient for a maximum ejection. A larger residual volume would therefore remain at the end of the next systole to which would be added the diastolic inflow. The resulting increased volume or tension would be conducive to more complete ventricular emptying, hence a "strong beat," and reduced residual end-diastolic volume.

Wiggers[4] has stated that mechanical alternation probably always involves the defection of some fractionate contractions during the small beats. He did not believe, however, that changes in the intensity of alternations signi-

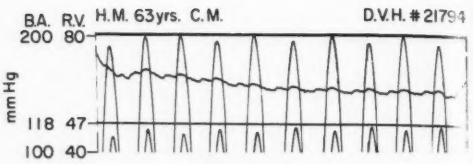

Figure 3

The period of discordant alternans outlined figure 2 has been enlarged to demonstrate the d cordancy.

fied quantal variations in the deletion of fra tionate contractions. Such changes in the ma nitude of the alternation might be induced l secondary dynamic factors that altered dia tolic distention and initial stretch.

Friedman and associates[5] demonstrated th importance of hemodynamic factors in mod fying the magnitude of mechanical altern tion. Alternans is exaggerated in certain pa tients by the erect posture, phlebotomy, and venous pooling plus tourniquets. It is dimin ished or abolished by recumbency, exercis digitalis, norepinephrine, transfusion of blood, and the application of external vascular support. These investigators concluded that a weakened or injured heart muscle might not contribute sufficient contractile strength to empty the ventricle efficiently unless extracardiac hemodynamic factors altered ventricular inflow or peripheral resistance.

Ryan and associates[6] observed that in 3 patients pulsus alternans was greatly diminished or virtually disappeared with advanced congestive failure. With partial cardiac compensation the alternans reappeared; when compensation was more complete the alternans again disappeared. Such observations suggested that there may be a critical range of ventricular filling pressure for ventricular alternation to occur.

The demonstration of discordant alternans would suggest that a defection of some fractionate contractions during the small beats is not of primary importance in this patient. It would seem unlikely that the defection would occur at times concordantly and then again discordantly in the 2 ventricles. A more likely explanation would appear to be that hemo

dy amic factors were altered by some unkn wn mechanism, so that one ventricle was m e completely distended while the other w s less completely distended. Because the m ocardium of both ventricles was "sick," the m e distended ventricle emptied more comp tely, whereas the less distended ventricle w s unable to empty completely because of insufficient initial stretch. A residual volume w uld therefore be present in the latter ventr le at the end of systole, which would summ te with the diastolic filling permitting more complete emptying during the next contraction. Discordant alternans would therefore exist. The occurrence of discordant alternans demonstrates that the 2 ventricles are capable of relatively independent behavior, if but for a few beats.

Summary

A patient with simultaneously recorded discordant pulsus alternans is presented. No similar example of this phenomenon has been found in the English literature.

The implications of this observation in elucidating the mechanism of pulsus alternans are discussed.

Summario in Interlingua

Es presentate le caso de un patiente in qui registration simultanee demonstrava in le duo circulationes le presentia non-synchronic de pulso alternante. Nulle simile exemplo esseva trovate in le litteratura de lingua anglese. Es discutite le signification de iste observation pro le clarification del mechanismo de pulso alternante.

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Feinstein, A. R., and Di Massa, R.: The Unheard Diastolic Murmur in Acute Rheumatic Fever. New England J. Med. 216: 1331 (June 25), 1959.

Auscultation of 359 patients referred from different sources in New York City to the Irvington House for rheumatic fever revealed 129 with diastolic murmurs appearing during the acute or early convalescent phases. In 14 patients the murmurs developed some time after admission. Of the 115 with diastolic murmurs detected on admission there were 31 patients in whom the murmur had not been recognized previously. These "unheard" murmurs were found in 9 per cent of patients referred from teaching hospitals and in 39 per cent of those referred from other sources. The authors point out that the detection of these murmurs at later examinations in a patient with rheumatic fever and the erroneous attributing of the cause of the murmur to new conditions may account for certain clinical paradoxes in rheumatic heart disease.

Sagall

SYMPOSIUM ON CONGESTIVE HEART FAILURE

The Clinical Management of Congestive Heart Failure

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TO control the manifestations of congestive heart failure effectively, treatment must be directed at correction of the basic derangements. Using improved technics modern investigators have shown conclusively that the central fault in congestive heart failure lies in the heart. Myocardial weakness, manifested by inadequate myocardial contractility, initiates the train of events of congestive failure. Within wide limits, the right and left ventricles are normally able to receive increased amounts of blood during diastolic filling and to expel the increased amounts into the pulmonic and systemic circuits. With the inception of heart failure, the ventricles fail to empty adequately during systole and the delivery of blood to the tissues is reduced. This failure to empty adequately is "forward failure." The residual blood in the ventricles at the conclusion of systole hinders diastolic filling. The blood accumulates in the atria, in the pulmonic and systemic veins, and in the lungs, liver, etc. This backward accumulation is "backward failure." Thus, the failure of the ventricles to empty adequately leads simultaneously to both "forward failure" and "backward failure."

The clinical manifestations that are diagnostic of heart failure include dilatation of the heart, a generally somewhat increased heart rate, cyanosis, gallop rhythm, the signs and symptoms of congestion of the lungs and liver, abnormal distention of the jugular veins, hepatojugular reflux, and edema of the legs in the absence of other causes such as varicose veins.

Congestive failure can be affected favorably by rest, digitalis, diuretics, salt and water regulation, sedation, and mechanical removal of edema fluid. Corrective surgery for valvular and congenital heart disease is now playing an increasingly important role. Finally, in euthyroid patients with intractable heart failure, radioactive iodine therapy has been found worthwhile.

Rest continues to be a fundamentally important therapeutic principle in the treatment of congestive failure. Attention to emotional as well as physical factors in attainment of rest is essential. The degree of therapeutic gain obtained through rest is proportional to the reduction of bodily activity. Usually the maximum benefit is derived from complete bed rest in the semirecumbent or sitting position with occasional use of a commode at the bedside. Certain patients, particularly those with pulmonary edema, achieve maximal comfort sitting in a chair, propped up by pillows, and leaning forward on an adjustable table. Elevation of the head of the bed on blocks or the use of a Gatch bed may afford considerable relief from dyspnea. Elastic stockings to decrease the discomfort of swelling and to prevent thrombophlebitis are to be considered. The alleviation of anxiety, the elimination of disturbing visitors, and effective nursing care may enhance the patient's recovery. By provision of maximal comfort to the patient the

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Supported in part by a grant (H-4151) from the U.S. Public Health Service.

metabolic requirements of the body are reduced: the work of the heart is lessened; the ventricular rate is lowered; the pulse deficit may be markedly diminished; and cardiac efficiency is increased. At times through this measure alone, dyspnea and cyanosis are favorably affected, and marked diuresis occurs. This diuresis is physiologic; isotonicity of body fluids is maintained without preponderant loss of cations or anions.

Digitalis is the most important drug in the management of congestive failure for it tends to correct the fundamental weakness of the cardiac contraction. The vigor of cardiac systole is increased, dilatation of the heart is lessened, the work output in relation to oxygen consumption, that is, "cardiac efficiency," is heightened.

Many satisfactory preparations of digitalis are now available. Qualitatively, the action of the various digitalis glycosides and the margin between the therapeutic and toxic ranges of doses are similar. Therapeutic action of all the glycosides is attained at approximately 50 to 60 per cent of the toxic dose.[1] No particular glycoside has been demonstrated to be superior although patients occasionally seem to tolerate one preparation better than another. The physician is well advised to select 1 or 2 preparations and through continued use to become thoroughly familiar with their pharmacologic characteristics under varied circumstances in many patients. A long-acting preparation, a short-acting preparation, and one that is suitable for emergency intravenous use are required.

Digitoxin is generally regarded as the long-acting drug of choice.[1] Standardization is more accurate and potency more uniform than with digitalis folia. Gastric irritation is less, absorption is more complete and uniform, and the cost to the patient is only very slightly more than that of the leaf. Digitoxin is available in 0.05-mg., 0.1-mg., 0.15-mg., and 0.2-mg. tablets, which are roughly equivalent to 0.05 Gm., 0.1 Gm., 0.15 Gm., and 0.2 Gm. of whole-leaf digitalis, a ratio of 1 to 1,000. When given by mouth, the action of digitoxin is usually discernible within 30 minutes; the maximum effect is achieved within 6 to 8 hours. The lessened gastric irritation with large doses of digitoxin has led to renewed interest in attempts at single-dose digitalization, but this technic offers no important advantage and has resulted in increased digitalis toxicity on the one hand and inadequate digitalization of many patients on the other. In this connection it should be realized that an average dose is necessarily inadequate or excessive for a significant proportion of the normally distributed population.

The average "digitalizing" dose for the hypothetical patient of 70 Kg. (154 pounds) is 1.2 mg. of digitoxin. Those patients, however, who require less than this amount, will experience serious toxicity from this dose. Some require 2 or even 3 times the average dose to secure the therapeutic effects. For most patients, determination of the proper dose of digitalis, in whatever form it is used, must be accomplished in accordance with the classic dictum of Withering: ". . . . let it be continued until it either acts on the kidneys, the stomach, the pulse, or the bowels; let it be stopped upon the first appearance of any one of these effects." In actual practice, aversion to food is usually the signal to be heeded, making unnecessary the more serious and distressing manifestations of digitalis intoxication. The risk of overdigitalization must, under certain circumstances, be accepted although occasional instances have been reported in which the first sign of overdigitalization was serious or even fatal toxicity.

In a patient who has not had any digitalis preparation for 10 days and who is not in emergency status, administration of 0.4 mg. as an initial dose is recommended. Subsequent doses of 0.2 to 0.4 mg. may be given at 4- to 12-hour intervals depending on the urgency of the situation, the body weight of the patient, and the therapeutic or toxic response. If the patient shows atrial fibrillation, quite precise guides are afforded by the pulse deficit and by the ventricular rate. Therapeutic response is gaged by improvement in clinical

signs and symptoms, particularly diuresis, lowered heart rate, and lessening of venous distention, dyspnea, and cyanosis. In occasional instances, observation of the characteristic electrocardiographic changes due to digitalis may be additional evidence of having attained the therapeutic level of digitalization. Following digitalization, the maintenance dose must be determined. Some patients require 0.1 mg. daily, others as much as 0.3 mg.

In emergency situations, in which rapid digitalization is indicated, and, particularly if one is not certain of the exact prior digitalization of the patient, a short-acting preparation such as lanatoside C, Digoxin, or ouabain is indicated. Lanatoside C in a dose of 0.8 mg. may be given intravenously followed by 0.4 mg. every 2 to 6 hours for 2 or 3 doses until the maximum therapeutic effect is achieved. The average total intravenous dose is approximately 1.6 mg. The duration of action is approximately 12 to 36 hours. Similarly, Digoxin may be administered intravenously in an initial dose of 0.5 mg. followed by 0.25 mg. every hour. The total intravenous digitalizing dose is usually 0.75 to 1.50 mg. Orally, the total dose is 2.0 to 4.0 mg., and the daily maintenance dose is usually 0.5 mg. but may vary from 0.25 to 1 mg. Children require approximately 50 per cent more digitalis than do adults on the basis of body weight.[2]

In general, intramuscular administration of digitalis preparations is contraindicated. Absorption in the presence of congestive failure is uncertain and local irritation may ensue. Except in emergency situations, oral administration of digitoxin usually satisfies all requirements. At times, one may be uncertain of the amount of digitalis taken by the patient during the previous week or 2. It is then advisable to give 0.2 mg. of digitoxin or its equivalent 2 or 3 times a day and observe the patient closely for signs of intoxication before each dose is given.

When congestive failure persists despite therapy, the possibility of inadequate digitalization and the advisability of administering additional amounts of digitalis must be considered. Underdigitalization may control the cardiac rate at rest, but may not prevent a disproportionate rise on effort. Even slight increases in dosage such as an additional 0.1 mg. of digitoxin every other day or 0.05 mg. daily may at times achieve distinct improvement. The risk of digitalis toxicity must be weighed and, at times, accepted despite the dangers of arrhythmias and nausea or vomiting. Under such circumstances, the use of a preparation with relatively short duration of action such as Digoxin possesses obvious advantages. Finally, it must be remembered that overdigitalization, particularly if many extrasystoles are induced, may affect congestive failure adversely. If digitalis toxicity occurs and particularly if it follows administration of mercurial diuretics or chlorothiazide, potassium salts such as potassium citrate or potassium chloride 2 Gm., 2 or 3 times daily, may be beneficial.

Sedation is usually accomplished with meperidine (Demerol), one of the barbiturates, or chloral hydrate. The sodium salts of the barbiturates and of other drugs should not be used in patients on low-salt intake unless they are included in the calculated intake. Morphine or its equivalents generally should be avoided because of their depressant effect on respiration and the cough reflex, except in certain conditions such as pulmonary edema. In the presence of marked pulmonary emphysema their use is dangerous. The judicious use of mild sedation during the day and obtaining restful nights for the patient are essential. Tranquillizing drugs such as meprobamate occasionally may be useful in tiding patients over periods of acute anxiety. Their continued use over long periods of time in conditions such as congestive failure entails the risk of depression and other side effects and is generally inadvisable.

Oxygen therapy by mask, tent, or nasal catheter is advantageous, particularly in the presence of cyanosis and severe dyspnea. In critical situations, it may be lifesaving. The choice of the method of administration will be influenced greatly by availability of oxygen

and of apparatus and by the reaction of the patient. A properly operating tent with effective cooling of the air and absorption of carbon dioxide may attain oxygen concentrations of 50 to 80 per cent. Use of the Boothby mask may enable inhalation of 90 to 100 per cent oxygen while the percentage attained by cellophane masks may range from 30 to 60 per cent depending on the accuracy of the fit of the mask and rate of oxygen flow. A soft rubber catheter inserted into the nasopharynx through the nostril with oxygen flow of about 2 liters per minute increases the oxygen concentration of the inspired air to a little over 30 volumes per cent. With a flow of 4 liters and double nasal catheters, 50 per cent oxygen can be introduced into the lungs. Care must be exercised to avoid insertion of the catheter into the esophagus. Examination of the patient and nursing care are made more difficult by apparatus for oxygen therapy. Some patients exhibit increased dyspnea, restlessness, and hyperventilation.

In patients with pulmonary emphysema and marked cyanosis, oxygen in high concentration may be hazardous. Respiration of some of these patients no longer is governed by carbon dioxide or hydrogen ion concentration. The carbon dioxide combining power of their serum plasma is greatly increased; respiration in these patients is governed by lack of oxygen. Oxygen therapy may remove the anoxic stimulus to respiratory and thereby induce respiration depression, coma, or even death. The respiratory rate and volume of patients therefore should be observed particularly when oxygen therapy is initially used.

Treatment of Edema

Consideration must now be given to the treatment of the edema itself. The chief guide in fashioning the optimum regimen is the response of clinical evidences of edema to treatment; the daily weight after urination and before breakfast each morning is the simplest and most accurate measure. This daily weight should be charted. If the patient is too ill to be weighed, measurements of fluid intake and urinary output are desirable. Determinations of vital capacity may be helpful in patients suffering primarily from pulmonary congestion. If massive edema is present, a daily loss of body weight of 2 to 4 pounds (1 to 2 Kg.) is preferable to inordinately large diureses of body fluid. Particularly in elderly men, large diureses may lead to acute distention of the bladder and urinary retention, especially if morphine or meperidine is also administered.

Sudden loss of large volumes of edema fluid may be attended by loss of considerable fixed base including sodium, potassium, and calcium.[3] Muscle cramps, marked weakness, nausea, vomiting, and digitalis toxicity may only add to the patient's woes. Predisposition to pulmonary infarction has also been reported under such circumstances. If the discomfort is considerable and is clearly due to inordinate diuresis, the administration of 1 to 2 Gm. of sodium chloride by mouth is to be considered. In occasional patients who experience nausea after mercurial diuretics, orange juice or potassium chloride or citrate by mouth, in doses of 2 to 4 Gm. administered during the 24 hours after injection, may be helpful.

Although a full discussion of the pathogenesis of edema is not feasible here, certain cardinal facts must be borne in mind. As previously stated, inadequate forward flow and backward accumulation with its increased venous distention and pressure predispose to accumulation of water and electrolytes in all the tissues of the body. The effects of these abnormal hemodynamics are particularly important on the kidneys; the renal factor in congestive failure is of decisive importance. When the output of blood to the tissues is reduced, the amount delivered to the kidney is lowered disproportionately to that of the rest of the body. Stasis occurs also in the veins of the kidneys, and the pressure in the renal veins is increased because of backward failure. The amount of the glomerular filtrate is markedly reduced. As this reduced amount of glomerular filtrate descends to the tubules, a greater than normal amount of fixed base, such as sodium, and of water is reabsorbed into the blood stream. The role of hormones

such as aldosterone and of other factors is discussed elsewhere in this Symposium.

The lessened glomerular filtration and increased tubular reabsorption are of cardinal importance in the pathogenesis of congestive failure and demand therapeutic correction. Digitalis promotes increased blood flow and glomerular filtration; diuretics lessen tubular reabsorption.

A lowered salt intake is prescribed. Initially, particularly if the patient is obese or well nourished, a simple dietary regimen of 4 to 6 glasses of milk, that is, 1,000 to 1,500 ml. of milk daily, may be employed. Approximately 1,000 to 1,500 calories and from 500 to 750 mg. of sodium are thus administered. A more limited sodium intake of 200 to 500 mg. is not infrequently necessary; low-sodium milk usually is available at approximately 50 cents per quart. Diets low in salt and containing more adequate calories and vitamins and other essentials may be prescribed according to the individual needs of the patient by utilizing the diets made available in the American Heart Association's *Recipes for a Low Salt Diet*. More liberal amounts of sodium chloride, up to 2 or 3 Gm., occasionally may be permissible in order to maintain nutrition, particularly if malnutrition and hypoproteinuria are present, and the patient tolerates daily administration of chlorothiazide. The use of salt substitutes enhances the palatability of the diet to some patients. Other condiments without sodium, such as pepper, paprika, mustard leaves, vinegar, cinnamon, and garlic, are permissible and very helpful. Supplementary vitamins and increased dietary protein are frequently advisable.

Water, sufficient to keep the patient comfortable, is permitted on the regimen of restricted salt intake. Usually up to 2,000 or even 3,000 ml. of water may be permitted; marked restriction is generally unnecessary. Under certain conditions, however, such as the "dilution syndrome" lowered intake of fluid is of great importance. Large amounts of 6 or more liters, as have occasionally been advocated, probably accomplish little and entail definite risks.

The mercurial diuretics are usually indicated initially in the control of severe congestive heart failure. The calcium rather than the sodium salts should be used for this purpose. One of the mercurial preparations containing mercury organically bound with theophylline in a dose of 2 ml. should be given deeply intramuscularly. Meralluride (U.S.P., Mercuhydrin) is frequently used. Administration early in the morning is advisable in order to obtain diuresis predominantly during the day. If the reaction of the patient is unknown and the situation is not urgent, an initial dose of 0.5 or 1 ml. should be given. In patients with poor absorption in edematous areas, the use of mercaptomerin (Thiomerin), which can be injected into the deltoid, is desirable. This drug may be used subcutaneously and is attended by less pain and can be self administered by the patient regularly if necessary. Prior preparation of the patient over one or more days by the daily administration of 3 to 4 Gm. of enteric-coated but absorbable ammonium chloride enhances the effects of the mercurial diuretics. In some patients the frequency of injections can be reduced by administering ammonium chloride intermittently, that is, 3 or 4 days in succession each week. Overdosage induces gastrointestinal symptoms and chloride retention with acidosis.[4-6] Intramuscular injections are to be avoided in patients receiving anticoagulant therapy.

Some patients exhibit sensitivity or idiosyncrasy to the mercurial diuretics. Pruritus, skin rashes, stomatitis, metallic taste, gastrointestinal disturbances, prolonged local pain, and induration at the site of injection may be encountered. These untoward reactions are frequently obviated by shifting to a different preparation and to smaller doses or by relying entirely on chlorothiazide. The antihistaminic drugs are at times effective in ameliorating the skin manifestations. British anti-Lewisite (BAL) may be used in the treatment of the toxic manifestations but should not be used simultaneously with the mercurials, since it blocks the renal tubular diuretic action.

In most cases, the administration of 1 or 2 ml. of the mercurial diuretic producing a loss of 3 to 4 pounds should be given every other day for 2 to 4 doses, with one of the acidifying salts, in addition, if necessary. When all signs of edema have disappeared and the weight reaches a resistant level, the "dry weight" of the patient has been attained. The interval between doses may then be lengthened by 1 or 2 days if not more than 2 pounds are regained in the next 48 hours. Every effort should be made to maintain the patient at about his dry weight. During long-term care of chronically ill patients, the dry weight may gradually decrease due to cachexia, while unrecognized extracellular fluid may accumulate. Therefore, the true dry weight should be re-evaluated every several months as the guiding point for therapy. To rely on recrudescence of dyspnea or edema of the legs or right upper quadrant distress is analogous to treating a diabetic patient with insulin only when he becomes acidotic or shows marked glycosuria. Patients may gain more than 5 or 10 pounds of edema fluid before edema of the legs or rales in the lungs become manifest.

In patients with moderate or slight congestive failure, chlorothiazide administered orally in doses of 0.5 or 1 Gm., once or twice a day, is a potent diuretic agent and may be substituted for mercurial diuretics. Sodium and chloride are excreted in approximately equivalent amounts; potassium excretion is increased and leads to hypokalemia after continued administration unless potassium supplements are given such as orange juice, potassium chloride, or citrate.

In patients who are in an emergency status or in severe congestive failure, mercurial diuretics are still our mainstay during the initial phase of treatment and chlorothiazide therapy is used subsequently to maintain dry weight. In patients with mild congestive failure chlorothiazide 0.5 Gm. once daily or every other day or for 4 or 5 days a week may suffice. The diuretic effect of chlorothiazide is mainly completed within 6 to 12 hours and therefore day-time diuresis can be achieved by morning administration. An intermittent schedule is less likely to be accompanied by excessive response or electrolyte imbalance. If chlorothiazide is used regularly to maintain the patient at a dry weight, it is usually unwise to restrict the daily dietary sodium chloride to less than 2 Gm., and supplementary potassium intake is usually indicated. As with other potent diuretics, the clinical course of patients who are markedly edematous and may already be in electrolyte imbalance should be guided by measurements of serum electrolytes. In some patients, excretion of chloride in relation to sodium is excessive, plasma bicarbonate level increases and alkalosis results. This is usually not severe and is infrequent when intermittent therapy is employed. Nausea, vomiting, diarrhea, dizziness, and paresthesia are rare side reactions following the use of chlorothiazide. Hydrochlorothiazide, recently made available, is administered in smaller dosage, but is similar in action to chlorothiazide.

The administration of potent diuretics is fraught with danger in the presence of active nephritis. This condition may at times be difficult to determine, particularly since albuminuria, casts, white cells and red cells in the sediment, and azotemia with the nonprotein nitrogen as high as 70 or 80 mg. per 100 ml. occur in congestive failure in the absence of significant intrinsic renal disease. When the nonprotein nitrogen blood level reaches 60 or 70 mg. per 100 ml., the possibility of intrinsic renal disease must be seriously considered. The specific gravity of the urine may be a helpful guide. A high specific gravity favors congestive failure, whereas a low specific gravity of 1.012 or less in the presence of oliguria raises the suspicion of significant renal pathology. Occasionally, it is impossible to rule out the presence of significant underlying nephritis. Under such circumstances small doses of chlorothiazide, such as 0.5 Gm., may be given and the effects noted on urinary output during the ensuing 12 hours as well as on the body weight the next morning. It must be remembered

that in the absence of a therapeutic response to mercurial diuretics in patients with congestive failure, toxic accumulation is prone to occur.

In past years, the use of cation ion exchange resins received considerable study. The unpalatability of the exchange resins, gastrointestinal distress, and their relative ineffectiveness militated against their use.

Acetazolamide (Diamox) is occasionally a useful adjuvant in controlling chronic congestive heart failure. It is a nonbacteriostatic sulfonamide that is a potent inhibitor of carbonic anhydrase. By promoting the excretion of bicarbonate ion, it leads to increased excretion of water and the cations, sodium and potassium. An alkaline urine is excreted and a metabolic acidosis occurs. When acetazolamide is given once a day, the duration of action is approximately 6 hours and considerable edema fluid is eliminated. During the subsequent 18 hours, renal compensation for the disturbance in acid balance occurs and the composition of the extracellular fluid is restored to normal. Consequently the next dose of the drug again induces a diuretic response. An effective single oral dose is 250 to 500 mg., 1 or 2 tablets or teaspoonsful of the syrup once a day in the morning. Its usefulness in promoting metabolic acidosis is discussed elsewhere in this Symposium. It is not of value in the edema of nephrosis or nephritis and should not be given to patients with hepatic cirrhosis. It may be used, however, in cardiac patients with renal disease.

With the advent of chlorothiazide, acetazolamide has found a lessened role in the therapy of congestive heart failure. If the drug is used, it is important to recall that increasing the dose does not increase the diuresis and may increase the incidence of drowsiness, paresthesia and, more rarely, fatigue, nausea, or vomiting. It should never be given to any patient with depleted sodium or potassium. As with most sulfonamides, acetazolamide has been noted to lead to rashes, fever, and leukopenia in a few patients who have received the drug over an extended period.

General Regimen of Management

In utilizing the individual therapeutic measures described above, namely, rest, digitalis, diuretics, sedation, and oxygen therapy, the physician must determine the optimal composite regimen for the particular patient, bearing in mind the clinical features, the gravity of the situation, the prior medical measures that have been invoked, and their effect.

If physical examination reveals dyspnea and respiratory embarrassment due to pleural effusion or ascites, paracentesis is indicated with the use of liberal amounts of procaine and a 16- or 18-gage needle. If the patient is seriously ill, if the venous pressure as indicated by venous engorgement of the cervical and other veins is high, if cyanosis is prominent and the hemoglobin level is normal or elevated, phlebotomy of 250 to 500 ml. may be indicated.

Acute Pulmonary Edema

This medical emergency occurs most commonly in patients with hypertensive heart disease. It may also occur during or after operation, particularly if saline infusions or blood transfusions have been administered rapidly or in a large quantity. Postoperative studies of the dynamics of the circulation in cardiac patients by Altschule and Gilligan[7] have shown that if physiologic saline or 5 per cent glucose in saline is given at rates below 15 ml. per minute, abnormally great or prolonged rises in venous pressure and marked increase in cardiac output or blood volume are avoided. Aside from their immediate effects, intravenous infusions that are repeated too often over a period of several days, favor the development of peripheral and pulmonary edema and cardiac pain. Paroxysmal dyspnea and cough may progress rapidly to frank pulmonary edema with intense cyanosis, struggling respiration, bubbling rhonchi and rales, and expectoration of pink, frothy sputum. The patient should be placed in Fowler's position or allowed to sit in a chair, where he will frequently be more comfortable than in bed. If the patient is struggling and excited and the situation is urgent, morphine

sulfate, 10 to 30 mg. given intravenously, may be lifesaving. If the patient has become stuporous, morphine should not be given. Aminophylline by slow intravenous injection of 0.25 to 0.5 Gm. may be effective in reducing bronchial spasm.

If the patient has not received a digitalis preparation for 10 days, lanatoside C may be given in doses of 0.6 to 0.8 mg. intravenously, followed by 0.4 mg. at hourly intervals until a favorable response is elicited. Ouabain or digoxin is preferred by some clinicians for rapid digitalization.

Oxygen therapy is urgently indicated. It should be given by means of an oxygen mask, humetered for positive pressure if available (humeter mask). A volume flow of 8 to 10 liters a minute achieves an oxygen concentration of 40 to 60 per cent. If a tent is utilized, a flow of 10 to 12 liters per minute of oxygen is necessary to attain a concentration of 50 to 60 per cent. If these methods are not available, a nasal catheter or, if the patient tolerates them, double nasal catheters should be employed. The use of ethyl alcohol introduced in the oxygen line to reduce surface tension of frothy pulmonary transudate has been proposed by Luisada and favorable results have been reported.[8]

With marked peripheral venous engorgement, the rather rapid removal of 500 ml. of blood should be performed. "Bloodless phlebotomy" likewise may be effective under such circumstances. Tourniquets, preferably blood pressure cuffs, should be applied to all 4 extremities. Three of these cuffs are inflated at a time to a pressure lower than the patient's diastolic pressure or to levels of 20 to 30 mm. Hg, if the higher pressures occasion discomfort. The amount of blood trapped in the limbs is presumably somewhat less at the lower pressures. Release of each cuff is done in rotation every 15 minutes to permit temporary supply of oxygenated blood to the limb.

Administration of a mercurial diuretic is frequently a valuable adjunct and, in the absence of contraindications, should be administered intravenously, intramuscularly, or subcutaneously shortly after the measures described above have been initiated, the route of administration depending on the agent and the urgency of the situation. If the intravenous route is employed, the possibility of slough from perivascular injection and the increased possibility of immediate toxic cardiac reactions must be borne in mind. To lessen the latter possibility, the dilution of the dose in 30 ml. of dextrose and water and slow injection over a period of 6 minutes are advisable.

The Refractory State

Occasionally we are confronted by the patient whose congestive failure stubbornly resists our usual therapeutic measures. Some patients with intractable congestive heart failure and only slight reserve, who are euthyroid clinically and by laboratory tests, may be benefited by induction of the hypometabolic state with radioactive iodine. In the experience of Wolferth, of Jaffe, and of the authors and their associates approximately one half of the patients experience worthwhile improvement. The details of the treatment including selection of patients, schedule of treatment, and clinical management are described elsewhere.[9-11]

Before accepting the possibility of true refractoriness due to inherent, irremediable cardiac weakness, however, we must ask ourselves the following questions.

Is the Refractory State Due to Specific Etiologic Conditions That Can Be Corrected?

Certain conditions increase the requirements of the body for blood. Hyperthyroidism, anemia, pregnancy, beriberi, arteriovenous aneurysms, and certain congenital malformations such as patent ductus arteriosus may be responsible for refractory congestive failure because they impose additional work on the heart. Treatment of such underlying conditions may remove the extra demand on the heart, permitting the normal needs of the body to be met more adequately. Cardiac arrhythmias may reduce the efficiency of the heart.

Tamponade from pericardial effusion or constrictive pericarditis may have been overlooked.

Hypoproteinemia not infrequently predisposes to edema in cardiac patients who have concomitant hepatic or renal disease or who have been anorexic or on a low-sodium diet.

Intercurrent infections have an adverse effect on the myocardium; indeed, acute myocarditis may be present. Steroid therapy may be indicated. Likewise, steroids may be indicated in the acute stage of rheumatic carditis. The possibility of pulmonary and other infections must be borne in mind, particularly subacute or acute bacterial endocarditis.

Pulmonary embolism and infarction occasionally may be responsible for refractoriness. In the presence of thrombophlebitis the use of heparin or Dicumarol is indicated. The high incidence of pulmonary embolism in bedridden patients with congestive failure has led some physicians to employ anticoagulant therapy in all such patients, provided, of course, no specific contraindications are present and adequate laboratory facilities are at hand.

In some patients, particularly those with acute pulmonary edema, the possibility of painless acute myocardial infarction must be considered. Extreme obesity with hypoventilation may be responsible for polycythemia and cor pulmonale. Recovery may be achieved by weight reduction.

Have We Restricted Sodium Sufficiently?

Congestion and edema of the lungs, abdominal viscera, and extremities are consequent to increased retention of sodium by the kidneys. A more rigid dietary restriction of sodium should be attempted. The Karell diet of 800 or 1,000 ml. of milk provides 400 to 500 mg. of sodium daily and is, therefore, usually unsatisfactory for refractory or severely decompensated patients.

A diet containing 50 to 100 mg. of sodium daily but furnishing adequate potassium, chloride, protein, and total calories may be used as a temporary expedient.

Has the Maximum Benefit Been Obtained from Diuretics?

If the edema of congestive failure is refractory to diuretics, several possibilities should be considered. The absorption of the mercurial diuretic after injection into edematous areas may be unsatisfactory. The use of a less irritating diuretic such as mercaptomerin into the arms or anterior thigh may be indicated. Preparation of the patient by use of one of the acidifying salts, such as ammonium chloride, or the use of aminophylline by mouth or rectally, beginning a day prior to, and continuing on, the day of injection may potentiate the effect of the mercurial diuretic. The use of xanthine diuretics or of urea by itself is rarely of value under such circumstances. Insistence on bed rest 12 hours prior to, and 18 hours after, mercurial diuretics may increase the urinary output.

Occasionally the situation is of such urgency, or the patient is sufficiently refractory to usual measures, to warrant intravenous administration of diuretics, which, however, on very rare occasions causes death. If indicated, the precautions previously outlined should be observed. The opinion has been expressed that the organic mercurials, which do not contain theophylline, such as mercaptomerin, are attended with less risk of arrhythmias and sudden death and are therefore preferable for intravenous use.

Chlorothiazide is also available in a dosage form suitable for intravenous administration. The duration of effect is relatively short, the major response being completed within 2 hours. The total effect is quantitatively less than that of a comparable oral dose. The dose of 0.5 Gm. is dissolved in 18 ml. of water and is then isotonic. The solution is alkaline, and extravasation is attended by untoward local reactions. It cannot be given by the subcutaneous or intramuscular route.

Is the Refractory State Due to the Low-Salt Syndrome or Other Electrolyte Imbalance?

The low-salt syndrome or other electrolyte imbalance should be suspected when the urinary volume is depressed, is not increased by

diuretics, and the patient experiences one or more of the following symptoms: weakness, drowsiness, headache, loss of appetite, thirst, nausea, vomiting, giddiness or syncope, muscle or abdominal cramps, gain in weight, and increased heart rate.[12] Cardiac psychosis may be a cardinal consequence and may be alleviated by therapy. Urinary volume is usually depressed 3 to 5 days prior to the onset of the symptoms and is associated with gain in weight and increased heart rate. These manifestations may be due to an undue loss of chlorides, sodium, potassium, calcium, and magnesium, or, under certain conditions such as after the administration of ammonium chloride, to retention of chloride and resultant acidosis with or without the loss of fixed base. When refractoriness to mercurial diuretics develops, further use should not be attempted until possible electrolyte disturbances have been corrected and careful evaluation of the clinical state, including the kidneys, has been made.

The various types of electrolyte imbalance and their treatment are described elsewhere in this Symposium.

Is the Refractory State Due to Nutritional Deficiency?

Anorexia, particularly on a limited dietary regimen, may lead to various deficiencies. Beriberi heart disease may develop insidiously and be responsible for refractoriness. Administration of thiamine may initiate improvement. Other vitamin deficiencies may be induced by loss of water-soluble vitamins during diuresis. Similarly low protein content of the diet, loss of protein in the urine or in thoracic and abdominal fluids, and the hepatic dysfunction intrinsic in congestive failure may lead to hypoproteinemia. This state may be exaggerated by the hypervolemia that further reduces the protein concentration. The use of serum albumin and protein hydrolysates low in sodium, plasma, or blood is indicated but usually the results are disappointing; prevention of nutritional deficiency is of far greater importance.

Are Mechanical, Surgical, or Other Measures Indicated?

Thoracentesis and abdominal paracentesis may at times greatly enhance diuresis and hasten convalescence. Large quantities of subcutaneous edema may be drained by inserting Southey tubes or 14-gage needles into the subcutaneous tissues above the ankle. After a few minutes the needles may be removed. Loose dressings may be applied to soak up the edema fluid or it may be permitted to drain freely into a receptacle. Procaine penicillin 300,000 units should be injected intramuscularly once or twice daily to prevent infection. When repeated drainage of large amounts of edema fluid is practiced, the concomitant loss of protein should be borne in mind. Less frequent removal of the fluid or increased intake of dietary protein may be indicated.

The present-day surgical approach of commissurotomy in advanced mitral stenosis offers suitable patients striking relief. Similarly, the correction of congenital abnormalities, of arteriovenous fistula, and the increasing scope of valvular surgery are important therapeutic advances. Some of the rarer causes of congestive failure or closely allied syndromes, such as atrial tumors, constrictive pericarditis, and aneurysm of the sinus of Valsalva, that are amenable to surgery are described elsewhere in this Symposium.

Conclusion

The modern regimen of salt restriction and mercurial diuretics and chlorothiazide has resulted in improved management of congestive heart failure, lessened disability, and greater longevity. But the use of a powerful tool, such as marked sodium restriction, also has introduced dangers. Sodium depletion and other electrolyte imbalance, particularly in patients with renal disease who are placed on a rigidly restricted sodium intake, have led to the development of weakness, anuria, and azotemia, which, when unrecognized, has resulted in fatalities. The use of mercurial and other diuretic agents in such patients has heightened the incidence of such reactions.

In other patients with renal impairment, mercurial diuresis has resulted in a disproportionate loss of chloride with hypochloremic alkalosis; continued administration of chlorothiazide may lead to potassium depletion as well as other electrolyte depletion. These untoward complications may, however, be avoided by awareness of their occurrence, early diagnosis, and immediate correction of the electrolyte imbalance. Great progress has been achieved also in preventive measures. The prevention of streptococcal infection, the effective treatment of syphilis, the early treatment of bacterial endocarditis, and the improved control of arterial hypertension are but a few of the important advances in recent time.

Summario in Interlingua

Le moderne regime de restriction de sal e administration de diureticos mercurial e chlorothiazido ha resultate in un reduction del invaliditate e un prolongation del superviventia post congestive disfallimento cardiac. Sed le application de un potente mesura therapeutic, como le restriction marcate de natrium lo es, ha etiam generate nove pericules. Le depletion del natrium e altere formas de imbalancia electrolytic—specialmente in patientes con morbo renal in qui le ingestion de natrium es rigidemente restringite—ha resultate in le disveloppamento de debilitate, anuria, e azotemia, e istos—in casos in que illos non esseva recognoscite—ha mesmo devenite responsabile pro le morte del patiente. Le uso de agentes mercurial e alteremente diuretic in tal patientes ha augmentate le incidentia de reactiones del typos mentionate. In altere patientes con defectuositate renal, le diurese mercurial ha resultate in un perdita disproportionate de chloruro e alcalose hypochloremic, e le continue administration de chlorothiazido pote resultar in un depletion de kalium e etiam de altere electrolytos. Tamen, iste complicationes adverse pote esser evitate, si on es conscie del facto que illos pote occurrer, si le diagnose es facite precocemente, e si le imbalancia electrolytic es corrigite immediatemente. Importante progressos ha etiam essite effectuate on le dominio del mesuras preventive. Le prevention de infectiones streptococcal, le efficace tractamento de syphilis, le precoce tractamento de endocarditis bacterial, e le meliorate regulation de hypertension arterial es solmente alicunes del importante passos in avante que ha essite effectuate in tempores recente.

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The Correction of Hyponatremia in Congestive Heart Failure

By E. Hugh Luckey, M.D., and Albert L. Rubin, M.D.

orrection of Hyponatremia in Congestive Heart Failure

LOW concentration of plasma sodium in a setting of congestive heart failure presents a difficult problem in management. This paper describes certain measures that we have found useful in treating patients under this circumstance. Numerous recent publications[1-3] have discussed in detail the various causes of the "low salt syndromes" or "dilution syndromes." We have nothing to add to these excellent summaries.

Low concentrations of sodium in the plasma of patients with edema due to congestive heart failure occur principally in individuals with advanced failure and, therefore, usually only in those who are relatively resistant to ordinary therapy. Because hyponatremia was usually associated with intensive therapy, early experience suggested that it was due to excessive sodium loss during diuresis, particularly with mercurial diuretics, in patients on unusually low sodium diets. Although each of these factors may play some part in the development of hyponatremia in some patients, there is now general agreement that the most important cause for this condition is an inordinate retention of water. Although plasma sodium concentration is low, total extracellular sodium remains higher than normal, and, obviously, water is present in an even greater excess. This consideration has led to the proposal of the term, "dilution syndrome[4]," instead of "low salt syndrome."

If it were possible to identify all of the elements that contribute to excessive retention of water in these syndromes, treatment could be much more rational. At the present time we must be satisfied to recognize at least 5 factors that are present, to varying degrees, in all patients who develop hyponatremia in the setting of congestive heart failure: (1) cardiac insufficiency, (2) evidence of renal impairment, (3) restriction of dietary sodium, (4) no restriction of water, (5) evidence of excessive humoral antidiuretic action.

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Cardiac Insufficiency

It is obvious that all patients with hyponatremia and edema due to heart disease have severe cardiac insufficiency. Since the extracardiac mechanisms responsible for the disturbance in handling water are the result, ultimately, of this cardiac failure, any measures which may be useful in improving cardiac efficiency should be helpful in correcting the hyponatremia. For this reason, initial attention should be directed toward a careful study of the nature of the heart disease including factors contributing to failure, and a reevaluation of the therapeutic regimen during which the hyponatremia developed. Fortunately, many of the episodes of hyponatremia develop during transient periods of deterioration of myocardial function such as occurs in a setting of myocarditis, intercurrent infection, pulmonary infarction, and other processes that superimpose an added burden on the failing heart. For this reason, these processes should be sought and treated as promptly and as vigorously as possible. Hyponatremia under these circumstances does not have the ominous significance of that occurring as an event in the natural, and usually terminal, phases of heart disease. Particular attention should be paid to adequacy of digitalization and to restriction of activity, but these matters are rarely critical in this group of patients.

When primary renal or liver disease accompanies heart failure, it has been our experience that hyponatremia occurs more frequently and is more difficult to control. In such instances efforts should also be directed,

when possible, toward direct improvement of the renal or liver function.

Evidence of Renal Impairment

There is frank evidence of renal insufficiency in patients who develop hyponatremia in congestive heart failure. This renal impairment is usually far more severe than that observed in ordinary congestive heart failure. Urea clearance is decreased, the blood urea nitrogen values are almost invariably elevated, administration of a water load results in no diuresis, body weight increases, and plasma sodium falls. Periods of hyponatremia and rising blood urea nitrogen frequently follow episodes of acute pulmonary edema. This sequence has suggested that sudden decrease of renal blood flow may be of importance in the pathogenesis of dilution and hyponatremia in some patients. Even though renal impairment is of major importance, its improvement must await amelioration of cardiac function and reduction in the excessive extracellular fluid volume. Nevertheless, all efforts should be directed toward the prevention of sudden decreases in cardiac output that may further compromise renal function.

Restriction of Sodium in the Diet

It is obvious that the development of hyponatremia in congestive heart failure is dependent on the relative availability of sodium and water. The total and relative amounts of these substances in the extracellular spaces at any one time will depend on the balances between intake and losses of each. For this reason rigid restriction of dietary sodium is certainly a contributor of some importance to the development of hyponatremia. If extrarenal losses are excessive, as through vomiting or diarrhea, further reduction in plasma sodium occurs. Even so, sodium balance is not of paramount importance in the majority of these patients, but the inability to handle a water load is.

Because the plasma concentration of sodium in these edematous patients is low even though the total extracellular fluid sodium is high, a suggested therapeutic measure has been the liberalization of dietary sodium intake or the slow, intravenous administration of hypertonic (3 or even a 5 per cent) sodium chloride. Early experience suggested that patients occasionally responded with a diuresis and a slow return of plasma sodium concentrations to normal. Further experience, however, has indicated the futility and danger of this procedure. Administration of sodium chloride usually does not produce a diuresis. The sudden increase in extracellular fluid sodium concentration (and osmotic pressure) withdraws water from body cells, causes intensive thirst, and commonly results in excessive fluid intake and progressive increase in body weight with persistent hyponatremia. In some patients in precarious failure, the increase in plasma volume from intravenous hypertonic sodium chloride may be sufficient to produce pulmonary edema and death. *In our opinion, intravenous hypertonic sodium chloride is never justified and should be condemned in the management of hyponatremia secondary to congestive heart failure.* A rare exception to this rule applies in congestive heart failure with slight edema and hyponatremia developing as the result of excessive extrarenal sodium losses.

Water Excess

Extracellular fluid volume and concentrations of electrolytes are maintained within narrow limits by the normal kidney. A defect in the renal handling of sodium is clearly demonstrable even in the early stages of congestive heart failure. It is commonly considered that water reabsorption follows sodium passively, and much evidence supports this concept. Nevertheless, even in the early stages of congestive heart failure, there are signs of retarded or defective renal handling of water loads[5] and in the later stages, this defective handling of water may be obvious and may dominate the clinical picture.

Excessive Humoral Antidiuretic Activity

The concept that there is excessive antidiuretic activity of humoral origin in patients with hyponatremia and edema has been well established by evidence that is summarized in

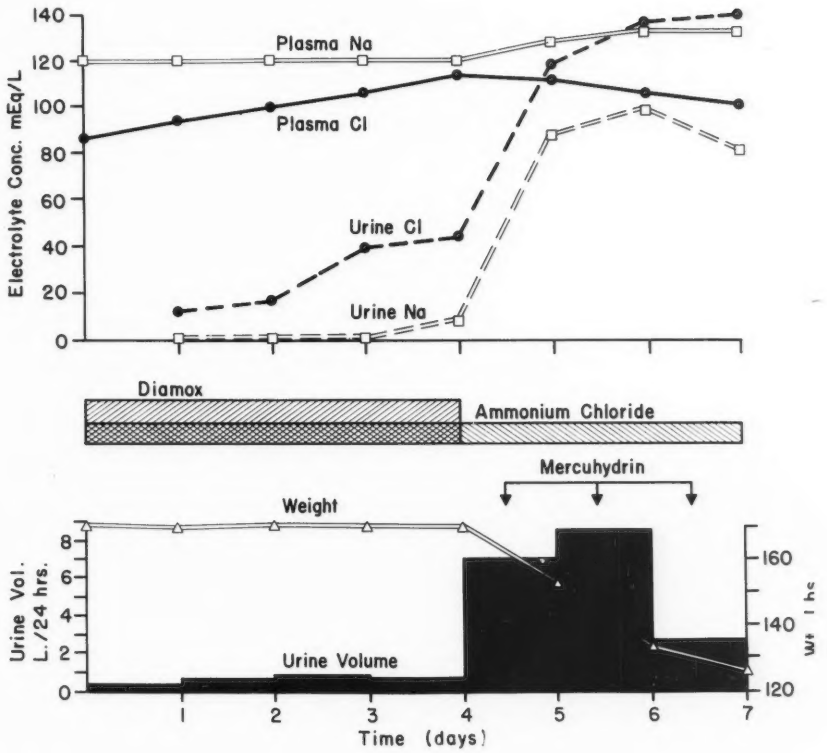

Figure 1

Case illustrating correction of hyponatremia by mercurial administration after elevation of plasma chlorides. Note step-wise increase in urinary chloride concentration and that urinary sodium concentration is always hypotonic. With diuresis, plasma sodium returns toward normal.

recent papers.[3, 6] Positive identification of this antidiuretic hormone as posterior pituitary in origin is not possible. Attempts to suppress the output of antidiuretic hormone with alcohol[7] in order to initiate a diuresis have been generally unsuccessful.

As has been emphasized, patients with hyponatremia and edema retain amounts of water that are excessive in proportion to sodium. Correction of hyponatremia requires the correction of this water-to-sodium relationship during diuresis.

Experience with the production of hyperchloremic acidosis for the treatment of resistant edema in heart failure[8, 9] has shown that during mercurial diuresis 24-hour urinary concentrations of sodium are often hypotonic with respect to plasma. In the patient with hyponatremia and hypochloremia, elevation of the plasma chlorides toward normal with non-sodium chloride salts results in an acidosis and a progressive increase in urinary chloride concentration. If fluids are restricted so as to approximate insensible losses, administration of a mercurial diuretic will result in a diuresis with urinary sodium hypotonic in comparison to plasma sodium. Such a diuresis over a period of days will result in a step-wise elevation of plasma sodium and a decrease in body weight.

Figure 1 illustrates the application of these principles and the futility of the use of hy-

pertonic saline in a patient with hyponatremia.

Case History

A 51-year-old white man was admitted to The New York hospital in severe congestive heart failure secondary to arteriosclerotic heart disease with previous myocardial infarction. He had been treated with bed rest, digitalis, salt restriction, and repeated mercurial diuretic injections.

Physical examination on admission revealed a dyspneic, orthopneic, cyanotic man with cardiac enlargement, bilateral pleural effusions, and 4+ peripheral edema. The venous pressure was markedly elevated. Plasma sodium was 131 mEq./L. and chlorides were 98 mEq./L. The blood urea nitrogen was 41 mg. per cent.

After 10 days in the hospital with strict continuance of the program followed at home, the patient remained unimproved. Urinary output was less than 1,000 ml. daily. Fluids were not restricted during this period.

Plasma sodium had fallen to 122 mEq./L. and plasma chloride to 87 mEq./L. Over the next 2 weeks the patient was given intravenous infusions of hypertonic (5 per cent) sodium chloride in amounts of 5 to 10 Gm. on 6 different occasions, which resulted in transient rises in plasma sodium and chloride concentrations. During this period, however, he remained unresponsive to mercurials and gained 13 pounds. The average fluid intake was 2,300 and the urinary output was 800 ml. At the end of this fortnight plasma sodium concentration was 120 mEq./L. and chloride level 94 mEq./L.

At this time administration of ammonium chloride was instituted in an attempt to restore responsiveness to mercurial diuretics. Fluid intake was restricted to less than 1,500 ml. and salt intake to 2 Gm. daily. A 25 per cent aqueous solution of ammonium chloride was given daily in 5 divided doses of 2 Gm. each. Acetazolamide (Diamox) was given in a single daily dose of 750 mg. for 4 days. When chloride concentration in the urine had risen over 40 mEq./L. on the fifth day, 2.0 ml. of meralluride were given daily for 5 days. Administration of ammonium chloride was continued, and potassium chloride was given on the second and third days (8 Gm. daily).

During the first 3 days of mercurial administration, there was a 42-pound loss of weight, and the urinary output rose to 1½ liters on the second day. The urinary sodium was always hypotonic with respect to the plasma, and consequently plasma sodium rose 12 mEq./L. during the 3-day period, to 132 mEq./L. The blood urea nitrogen decreased to 18 mg. per cent. The patient improved dramatically.

Discussion

The mechanism through which this "autogenous" correction of hyponatremia occurs is illustrated in figure 2. It may be noted that the rapidity of change in plasma sodium is a function of the daily net change in sodium balance versus water balance. In general, the larger the diuresis the more rapid is the correction of hyponatremia.

Experience with this procedure has now been extended to a group of patients sufficiently large to warrant certain general comments. First, without question, in our hands this technic is the most reliable and safest for the correction of hyponatremia in patients with congestive heart failure. Second, the principle is similar to that which underlies the production of hyperchloremic acidosis with chloride salts to restore responsiveness to mercurial diuretics in refractory patients without hyponatremia. The difference in application is due to the presence of both hyponatremia and hypochloremia. Chloride salts other than sodium chloride will produce an acidosis in patients with hyponatremia even though the chloride level has not reached normal. This is owing to the displacement of bicarbonate by the disproportionate, though not elevated, level of plasma chloride compared to the unchanged low level of plasma sodium. In this setting of a disproportionate elevation of the plasma chloride *even though hyperchloremia and even normal levels of plasma chloride cannot be achieved,* urinary chloride concentration will rise and the patient may

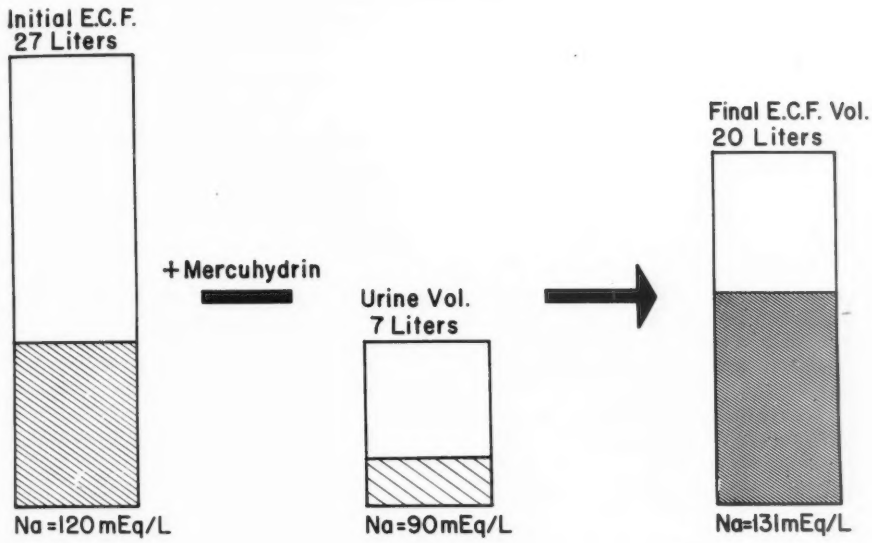

Figure 2

Sodium "gain" by body as a result of diuresis of urine that is hypotonic for sodium with respect to the extracellular fluid (ECF) can be calculated as 120 (ECF con./L.)—90 (urine conc./L.) × 7 (liters of urine) = 210 mEq. of sodium available for redistribution in the ECF remaining after diuresis. (Reproduced with permission from Rubin, A. L., and Braveman, W. S.: Treatment of the low salt syndrome in congestive heart failure by the controlled use of mercurial diuretics. Circulation **13:** *655, 1956.)*

become responsive to mercurial diuretics. Further, during this responsive diuresis, urinary concentrations of sodium are hypotonic in relation to plasma, thus resulting in a stepwise rise in plasma sodium concentration.

Because of the precarious failure in this group of patients and the ease with which acidosis may be produced with ammonium chloride or comparable chloride salts, great care is required in both clinical and laboratory observations during the application of this procedure. The dire prospects in this group of seriously ill patients justify the use of a procedure with the potential dangers inherent in this method. In our experience, however, this method is effective and the dangers involved in its application are much less than those associated with the use of infusions of hypertonic sodium chloride.

Although the representative case in figure 1 illustrates the use of ammonium chloride in combination with acetazolamide for elevation of the plasma chlorides, experience has indicated an even more satisfactory method. The contribution of acetazolamide to the elevation of the plasma chloride is minor, and we no longer consider it necessary to give this drug along with the chloride salt. Further experience with ammonium chloride has revealed a significant incidence of intolerance to the dosages of 10 to 12 Gm. required in this procedure. This intolerance may be simple gastrointestinal irritation as the result of ingestion. In addition however, in patients with moderate to severe hepatic insufficiency, this drug may precipitate flapping tremors or frank coma, which are apparently related principally to ammonium ion toxicity. Both calcium[10] and potassium chloride have been used as substitutes for ammonium chloride and although their administration is followed by elevation of the chloride level, each has definite disadvantages. Calcium chloride is even more irritating to the gastrointestinal tract than is the ammonium salt; potassium chloride is usually well tolerated, but in patients

with significant renal insufficiency and low urinary volumes, there is danger of producing dangerous hyperpotassemia if large amounts of potassium salts are given.

Occasionally the total doses of chloride ion can be divided between ammonium, calcium, and potassium salts, and can be well tolerated when a similar amount of chloride as a single salt cannot be taken. Fortunately we now have available a chloride salt with minimal gastrointestinal side effects and none of the disadvantages of the ammonium, calcium, or potassium ions. This is the monohydrochloride of L-lysine.*

Data to be published[11] indicate that plasma chloride levels may be elevated consistently and safely with this salt. Its only disadvantage is the relatively large dose on a weight basis that must be used to deliver an adequate amount of chloride ion. Whereas ammonium chloride has 18 mEq. of chloride per Gm., calcium chloride a comparable amount, and potassium chloride 14 mEq. per Gm., lysine monohydrochloride contains only 5 mEq. per Gm. and requires the administration of approximately 40 Gm. to elevate the plasma chloride to a level comparable to that achieved with 10 to 12 Gm. of ammonium chloride. This large dose is well tolerated when given with fruit juices. Although slight diarrhea is not uncommon during the first few days of treatment, this usually subsides gradually. No untoward effects of the lysine ion have been observed.

With return of plasma sodium level to normal, and loss of edema fluid, it is not uncommon to observe marked clinical improvement and, with careful attention to treatment, maintenance of relatively stable compensation for many months.

Summary

Hyponatremia in congestive heart failure occurs principally in the terminal phases of the natural history of heart disease. Fortunately, in some instances it may occur as a transient event in a setting of sudden deterioration in cardiac function. In such instances, it may be reversible.

The most important factor in the occurrence of hyponatremia in these patients is an inordinate retention of water. Thus, the hyponatremia is the result of dilution.

Correction of hyponatremia requires the elimination of water in excess of sodium. The futility and dangers of the use of hypertonic sodium chloride are emphasized.

A method of controlled administration of mercurial diuretics after elevation of the plasma chlorides toward normal with consequent production of acidosis with chloride salts is reviewed. Diuresis following this procedure results in sodium losses in urine that are hypotonic in relation to plasma. The plasma sodium gradually returns to normal, and the patient progressively loses weight.

Summario in Interlingua

Hyponatriemia in congestive disfallimento cardiac occurre principalmente in le phases terminal del historia natural del morbo cardiac. Felicemente, in certe casos illo pote occurrer como evenimento transitori in un situation characterisate per le deterioration del function cardiac. In tal casos il es possibile que illo es reversibile.

Le plus importante factor in le occurrentia de hyponatriemia in iste patientes es un excessive retention de aqua. Assi le hyponatriemia es le resultato de dilution.

Le correction de hyponatriemia require le elimination de aqua in excesso del natrium. Es sublineate le futilitate e le pericul del uso de hypertonic chloruro de natrium.

Es presentate un revista de un methodo de administration controlate de diureticos mercurial post le elevation del chloruros plasmatic verso nivellos normal con le production consequente de acidosis con sales de chloruro. Le diurese post iste manovra resulta in perditas de natrium in urina que es hypotonic in relation al plasma. Le nivello plasmatic de natrium retorna gradualmente a valores normal, e le patiente perde progressivemente in peso.

*The L-lysine monohydrochloride was supplied by the Lysine Division of the E. I. duPont de Nemours & Co., Wilmington, Del.

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A Clinical Consideration of Cor Pulmonale

By RÉJANE M. HARVEY, M.D., AND M. IRENÉ FERRER, M.D.

Definition

THE term cor pulmonale is generally used to define the cardiac complications of certain forms of lung disease. From knowledge gathered in the recent past, it is apparent that a number of disease processes that attack pulmonary function in a variety of ways can produce circulatory embarrassment. The mechanisms by which they do so may be fundamentally different and indeed the lungs themselves need not be directly involved. The terms cor pulmonale or pulmonary heart disease are far from ideal, since they imply cardiac disorders secondary only to pulmonary parenchymal disease, whereas the name should be more inclusive and encompass cardiac abnormalities stemming from any form of pulmonary dysfunction. It is therefore suggested that the name cor pulmonale always be coupled with the responsible etiologic agent; for example, cor pulmonale due to chronic obstructive pulmonary emphysema, due to multiple pulmonary emboli (acute or chronic), due to exogenous obesity, due to berylliosis, due to poliomyelitis, etc. Inasmuch as many of the circulatory abnormalities and the cardiac enlargement itself may be reversible in some of these instances, it seems wise to eliminate the terms acute, subacute, or chronic as applied to these circulatory complications and use them solely in relationship to the respiratory illness. Cor pulmonale would then be diagnosed only when evidences of right ventricular enlargement or failure are, or have been, shown to be present. Physiologic complications, such as anoxia, hypercapnia, polycythemia, pulmonary hypertension, could also be included in the formulation of the diagnosis. The format of the New York Heart Association lends itself admirably to this purpose. The functional and therapeutic classification would be determined not only by the state of the circulation but also by the state of the pulmonary function. The formal declaration would thus represent a complete description of the cardiopulmonary status of the patient. This diagnostic expression could even be used to indicate potential cor pulmonale before such a complication occurred. A few examples are given below.

Etiologic: Cor pulmonale due to chronic pulmonary emphysema.
Anatomic: Enlarged heart (right ventricle), enlarged pulmonary artery.
Physiologic: Pulmonary hypertension, anoxia, hypercapnia, secondary polycythemia, normal sinus rhythm, cardiac insufficiency.
Functional and Therapeutic: IV-D.

When such a patient has been adequately treated his diagnosis might appear as:

Etiologic: Cor pulmonale due to chronic pulmonary emphysema.
Anatomic: —
Physiologic: Anoxia, normal sinus rhythm.
Functional and Therapeutic: II-C.

Another example follows:

Etiologic: Cor pulmonale due to pulmonary emboli, multiple, recurrent.
Anatomic: Enlarged heart (right ventricle), enlarged pulmonary artery.
Physiologic: Pulmonary hypertension, normal sinus rhythm.
Functional and Therapeutic: III-C.

The crux of the definition of cor pulmonale given above lies in the demonstration of cardiac enlargement or failure in association with a disease process known to attack primarily the lungs or some aspect of the act of

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Supported by research grant H-2001 (C4) from the National Heart Institute, National Institutes of Health, U. S. Public Health Service.

reathing and in so doing to compromise right entricular function. It is clear that the presnce of pulmonary artery hypertension *per se* oes not constitute evidence of cor pulmonale. ndeed, there are many conditions that prouce pulmonary hypertension, e.g. congenital eart disease, mitral stenosis, left ventricular ailure, in which the basic abnormality is not disturbance of pulmonary function. Therefore these cardiac states should not be included under the heading of cor pulmonale. urthermore, it is now certain that all pulmonary disorders which induce mild or even moderate pulmonary hypertension do not necessarily go on to the complication of right heart involvement. The right ventricle has great adaptability and pulmonary artery pressure elevation alone may not, ipso facto, precipitate a disturbance in its function. An analogous situation obtains in the relationship of systemic hypertension to changes in the left ventricle.

Mechanisms

There are 2 basic mechanisms that lead to cor pulmonale: (1) alveolar hypoventilation* with moderate or severe anoxia and hypercapnia leading to pulmonary vasoconstriction, hypervolemia, and increased cardiac output, or (2) anatomic curtailment of the pulmonary vascular bed or a combination of these factors. Alveolar hypoventilation may result from lesions that involve the nervous system, the chest cage, or the bronchopulmonary apparatus. Central nervous system lesions that lead to depression of the respiratory center and right heart failure are rare and one hears of these in single case reports.[1] Spinal cord lesions, peripheral polyneuritides as well as the muscular dystrophies may also lead to alveolar hypoventilation when the muscles of respiration are involved. Structural deformities of the chest cage due to kyphoscoliosis[2] or surgery may disturb ventilation sufficiently to induce severe alterations in gas exchange and hence produce circulatory complications. The mechanics of breathing in such patients, however, are rarely faulty enough of themselves to produce profound hypoxia and hypercapnia. These disturbances in gas exchange are more likely to appear when the breathing difficulties are associated with some other disease such as emphysema, bronchitis, or pneumonia. Although the mechanisms responsible for the hypoventilation associated with exogenous obesity[3] are not fully understood, the primary disease is not of the lung parenchyma itself. In many of these instances of alveolar hypoventilation the lung parenchyma and vasculature may be virtually normal and the train of circulatory complications stems entirely from the disorders of gas exchange. Although there is some lung distention and even parenchymal destruction in patients who develop circulatory abnormalities with the disorders of bronchopulmonary function known as emphysema, alveolar hypoventilation is also the primary agent and not an anatomic reduction of the vascular bed. This is evident from the facts that the disturbances of the circulation are reversible and that pathologic examination indicates that widespread destruction of the vasculature is not characteristic of such lungs. Although most instances of cor pulmonale are seen in adults, children may also suffer from this disease. The excessive and thickened bronchial secretions produced in patients with cystic fibrosis of the pancreas may lead to severe alveolar hypoventilation. Acute diffuse bronchiolitis in children may also result in marked interference with ventilation and gas exchange, and hence in cardiac failure.

Anatomic curtailment of the pulmonary vascular bed as the primary cause of cor pulmonale is rare. This is so because there are very few diseases that attack the vascular bed

*Alveolar hypoventilation is used in this paper as a imple term to characterize a somewhat complex type f disturbance in ventilation perfusion relationships nd does not imply generalized or uniform underentilation of alveoli. Actually some alveoli may be oorly ventilated, others well ventilated, and still thers hyperventilated; but perfusion to these areas s not correspondingly affected and indeed may be ell maintained regardless of how the alveoli are entilated. Hence if a large area of the lung is oorly ventilated but well perfused the net result is disturbance in gas exchange.

so extensively as to reduce its area to a critical degree. It should be remembered that removal of one lung does not lead to right heart failure. Hence lesions that induce cor pulmonale solely by a reduction in the capacity of the pulmonary vascular bed must eliminate more than 50 per cent of this area. Among those that may do so are multiple or massive pulmonary embolization, the pulmonary arteritides, and certain of the pulmonary fibroses, particularly those producing the syndrome of alveolar-capillary block. It is difficult to classify the entity known as primary pulmonary hypertension, since so often the final examination in these subjects suggests that they were victims of multiple pulmonary emboli. Silicosis is one of the more frequently encountered fibrotic diseases associated with cor pulmonale. It has been assumed that these fibrotic lesions induce pulmonary hypertension and thence right heart failure. Closer inspection has indicated, however, that it is the patient with combined silicosis and emphysema who more usually develops circulatory disease.[4, 5] Moreover, it has been shown that the circulatory complications can be reversible as the anoxia secondary to alveolar hypoventilation lessens; this strongly suggests that anatomic lesions may not be the chief offenders and that the emphysema is at the root of the difficulties.[4, 6]

Cor pulmonale is not seen as a result of uncomplicated bronchiectasis, lung abscess, or pneumonia. Of course, if any of these diseases is accompanied by emphysema or any other cause of anoxia, right heart failure may follow. Similarly, uncomplicated pulmonary tuberculosis does not produce cor pulmonale even with extensive destruction of the parenchyma, although in some few cases mild pulmonary hypertension at rest or during exercise does exist.[7, 8] However, in the presence of abnormal chest mechanics due either to marked pleural fibrosis or to the results of chest surgery, ventilatory insufficiency in these tuberculous subjects may progress to an anoxic phase and then right heart involvement may occur.

Specific Disease Processes Responsible for Cor Pulmonale

Diseases That Produce Alveolar Hypoventilation and Cor Pulmonale

Emphysema

Chronic pulmonary emphysema is by far the commonest cause of cor pulmonale. On the other hand, not every patient with emphysema develops circulatory abnormality. This is well illustrated by the statistics collected by Dr. Anne L. Davis in the Emphysema Clinic of the First (Columbia) Division at Bellevue Hospital.[9] Of 114 patients who are followed regularly in this clinic and are known well not only clinically, but also from the point of view of pulmonary function, only 23 (20 per cent) have, or have had, a diagnosis of cor pulmonale. In an additional 5 subjects this diagnosis is being entertained but is as yet not confirmed. The sex incidence is striking. Of the 114 patients in this clinic, only 9 are female and, of these 9, 2 have cor pulmonale. Thus in this small but well-studied group, emphysema is much commoner in men, (92 per cent of this clinic population) but cor pulmonale occurs in 20 to 23 per cent of emphysematous patients regardless of sex.

The incidence of cor pulmonale in a general cardiac population is difficult to ascertain. In Sheffield, England, and in Belgrade, Yugoslavia, 25 and 16 per cent of cardiac patients in heart failure were found to have cor pulmonale. In Buenos Aires 3.3 per cent of general admissions to a cardiac clinic were so designated.[10]

A most interesting example of the importance of cor pulmonale due to emphysema in another part of the world, namely New Delhi, India, is found in the statistics provided by Padmavati.[11] In a 5-year survey (1950-1955) she found an incidence of cor pulmonale in the hospital admissions of 16.6 per cent of all cardiac cases, in contrast to 39.1 per cent for rheumatic and 11.3 per cent for degenerative heart disease. There were a larger number of women in this group as compared to western figures, as well as a number of adolescents suggesting that this was in a sense a family ill

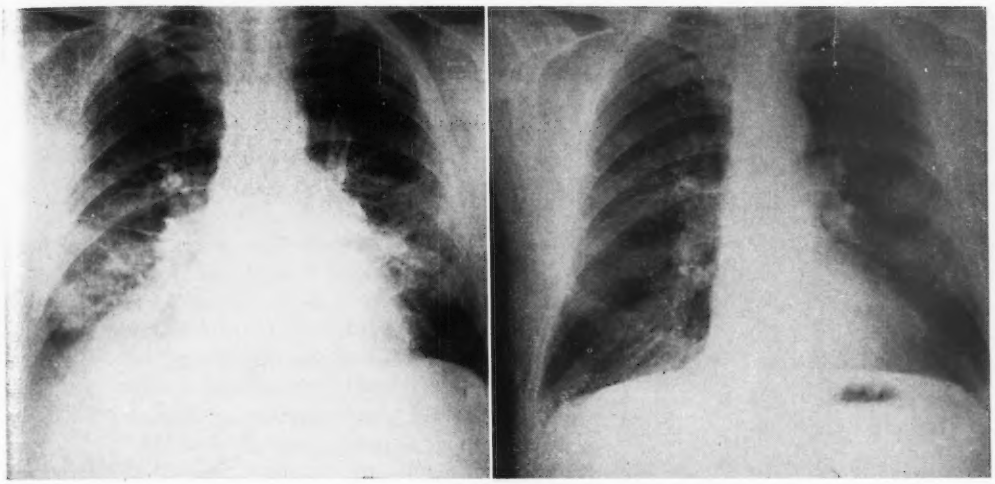

Figure 1

X-rays of a 63-year-old man (W.W.) with emphysema and cor pulmonale. When in full-blown cardiopulmonary failure the x-ray (left) *showed extensive pulmonary infection and cardiomegaly. Right ventricular pressures were 46/7. On recovery 2¼ months later* (right) *the lungs showed much less infiltration, no obvious blebs or bullae, and there was a decrease in heart size. The right ventricular pressures were 25/2. This chest film remained unchanged until his death from pneumococcus meningitis, 19 months after his first admission. The heart showed dilatation of the right ventricle but no hypertrophy.*

ness. This group was made up of farmers and housewives. Padmavati suggested that the emphysema and bronchial disorders that predominate as the pulmonary causes of the heart condition are largely the consequence of desperate poverty and poor housing conditions. Many of these individuals in one family live in 1 or 2 rooms that have no ventilation and are filled with smoke from cow-dung fires. In addition, cotton spinning is also done in this room and the women are thus exposed to the respiratory tract irritation produced by fine cotton fluff.

It is essential to determine the common denominator in patients with emphysema who develop cor pulmonale. It is now well recognized that cor pulmonale will appear only in those subjects who have hypoxia and hypercapnia as a result of severe alveolar-respiratory insufficiency. This alveolar hypoventilation stems from bronchiolar obstruction, decreased lung elasticity, and fixation of the chest cage, which combine to interfere with gas distribution to the lungs. When arterial oxygen saturation at rest falls below 80 to 85 per cent and carbon dioxide tension rises, then one finds disturbances in the circulation[12] and one or more of the following appear: a rising cardiac output, pulmonary hypertension, and an elevated hematocrit level. Although the exact mechanisms whereby anoxia elicits these changes are not fully known, there seems little doubt that it is the chief offender and with its relief comes a restoration to normal of the circulatory function. Thus the reversibility of the abnormal circulatory findings confirms the basic role of anoxia and minimizes the influence of the anatomic changes of the vascular bed.

Destruction of the lung vasculature is not an important factor in inducing the circulatory complications in emphysema because it is not extensive. This is evident from inspection of these lungs by x-ray and at necropsy. On x-ray these patients do not necessarily show large bullae, blebs, and cysts and indeed may show none of these. Figure 1 illustrates the roentgenograms in one such patient. This par-

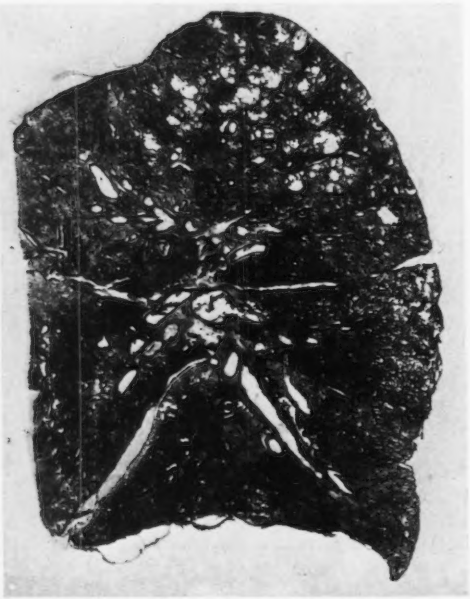

Figure 2

Sagittal section of the right lung of patient in figure 1. This specimen was prepared according to the technic of Gough by Dr. John Cromie, Department of Pathology, Bellevue Hospital. The right side of the section is the posterior surface of the lung.

ticular subject died of pneumococcus meningitis a number of months after these x-rays were taken. Necropsy examination of his lungs showed that he had emphysema (fig. 2), but the lung destruction was not marked and indeed large areas were free of alveolar disruption. The striking findings were evidences of bronchitis, bronchiolitis, and bronchopneumonia. Although it is true that the curtailment of the vascular bed seen in emphysema is not the sole, or even an important factor in the production of pulmonary hypertension, it may play a contributing role when the patient is under such stress as exercise or hypoxia.

The clinical picture of the emphysematous subject who develops cor pulmonale is a fairly distinct one. These individuals are usually in the fourth to the sixth decade when first seen and often give a history of chronic cough, bouts of bronchitis, and mild dyspnea on exertion, which becomes severe when associated with respiratory infections. Paroxysmal nocturnal dyspnea is commonly encountered in these patients but, unlike that of the subject with left ventricular failure or mitral stenosis, is relieved by cough if it is productive of sputum. Weight loss of a considerable degree may occur. These evidences of pulmonary disease may have been present from 5 to 10 years. Only very rarely does one encounter a patient with a history of bronchial or allergic asthma and cor pulmonale. In the past 13 years at Bellevue Hospital we have only found 1 such patient. Many patients state that their physicians told them they had asthma, but this began in their forties or fifties. It is likely that the evidences of obstructive breathing which these patients showed was termed "asthma" by their physicians. However, obstructive breathing is not peculiar or particular to bronchial asthma—it is also a major manifestation of emphysema.

To return to the patients' histories, despite cough and dyspnea they were able to continue their usual activities until a very bad "cold" or a "severe bout of bronchitis" or "pneumonia" precipitated extreme dyspnea, restlessness or somnolence, and ankle edema. Occasionally severe emotional tension will precipitate a period of marked bronchospasm and anoxia. Evidences of circulatory embarrassment are usually manifest only shortly before admission. Thus 2 salient traits characterize the history in such persons. First, the symptoms of their pulmonary disease were present for a considerable although variable period of time before cardiac disability was apparent. Second, their pulmonary disease was not rapidly or continuously progressive; rather it was marked by periods of remission. Unfortunately there is no symptom which marks the onset of the early circulatory complications of emphysema, and all too often it is not until hepatomegaly and edema are present that our attention is directed to the circulation. It is now known that a rising cardiac output, pulmonary hypertension, and an elevated hematocrit value antedate the manifestations of congestive failure[12] and are also well correlated with the level of arterial oxy

general saturation. A change in arterial blood gases should raise the suspicion that circulatory complications may develop. The onset of bronchitic or pneumonic infection, a frequent event in such cases, may be the cause of deterioration in gas exchange.[13] Minor increases in heart size as seen on serial films or a rising hematocrit level would confirm such a suspicion. Most of the patients with overt cor pulmonale due to emphysema have hypercapnia and moderate to severe anoxia (saturation less than 80 per cent). One must remember, however, that the resting level of arterial oxygen saturation alone is not an absolute criterion of impending circulatory dysfunction as levels as low as 60 per cent can be found without it. It is probable that the duration of the hypoxic and hypercapneic state, the rapidity of its onset, its severity, as well as the physical activity engaged in by the patient, determine whether or not circulatory complications appear. A patient whose arterial oxygen saturation suddenly drops to a low level (e.g. 60 per cent) but who is confined to bed and vigorously treated may escape circulatory sequelae in large measure because his severe hypoxic state is transient. On the other hand the working man, unaware of the precarious situation may progress into them fairly rapidly. It is true that his saturation at rest may be above 80 per cent but on exertion it may fall to much lower levels.

On physical examination of the patient with cor pulmonale due to emphysema one finds a dyspneic, tachypneic, orthopneic, and cyanotic patient who is coughing ineffectively and bringing up thick, tenacious sputum with difficulty. His eyes may be froglike, protuberant, injected, and chemotic. The neck veins are engorged and fill from below. It should be remembered that the neck veins of many patients with emphysema but without heart failure are distended as a consequence of the marked changes in intrapleural pressure. Retrograde filling will distinguish the ones with an elevated venous pressure. The chest resembles a rectangle more than any other shape because the manubrium is raised upward and forward, and there is rounding or "buffalo hump" in the back. The patient uses the accessory muscles of respiration. The authors have never seen Cheyne-Stokes breathing in cor pulmonale in the presence of carbon dioxide retention. The lungs are filled with wheezes, rhonchi, and rales unless bronchospasm is extreme, in which case the chest is remarkably quiet and breath sounds are almost inaudible. Hydrothorax does not appear in this form of right heart failure. If pleural fluid is present, another cause such as pulmonary infarction or infection should be sought. The heart is enlarged, the rhythm is regular and rapid, and the pulmonic second sound may be equal to or greater than the aortic second sound. A systolic murmur may be heard over the pulmonic or apical areas. A gallop is often present over the ensiform. The liver is enlarged but ascites of any magnitude is not present. In congestive failure the extremities may or may not show considerable edema. This type of edema should not be confused with that due to peripheral circulatory stasis, which is a very common finding in the patient with severe pulmonary insufficiency not in cardiac failure who, bedridden because of dyspnea, sits constantly with his legs over the side of the bed. The fingers rarely show unequivocal clubbing although cyanosis may be marked.

The x-rays of the chest reveal low diaphragm, increase in intercostal spaces, and enlarged hearts. The cardiac enlargement may be quite marked, but is confined to the pulmonary arteries, right ventricle, and right atrium (fig. 1). One occasionally sees a patient in the fullblown congested state whose heart size *appears* to be within normal limits. However, the small vertical heart of the emphysematous patient on dilatation may not be very large and it is only by comparison with previous films that cardiomegaly can be defined. If this information is not available, cardiomegaly may only be apparent after recovery from failure, when the heart returns to its previous small size. The marked changes in heart size as the patient goes in and out of cardiac failure and the rapidity with which this may happen (fig. 3) lead one to believe that dila-

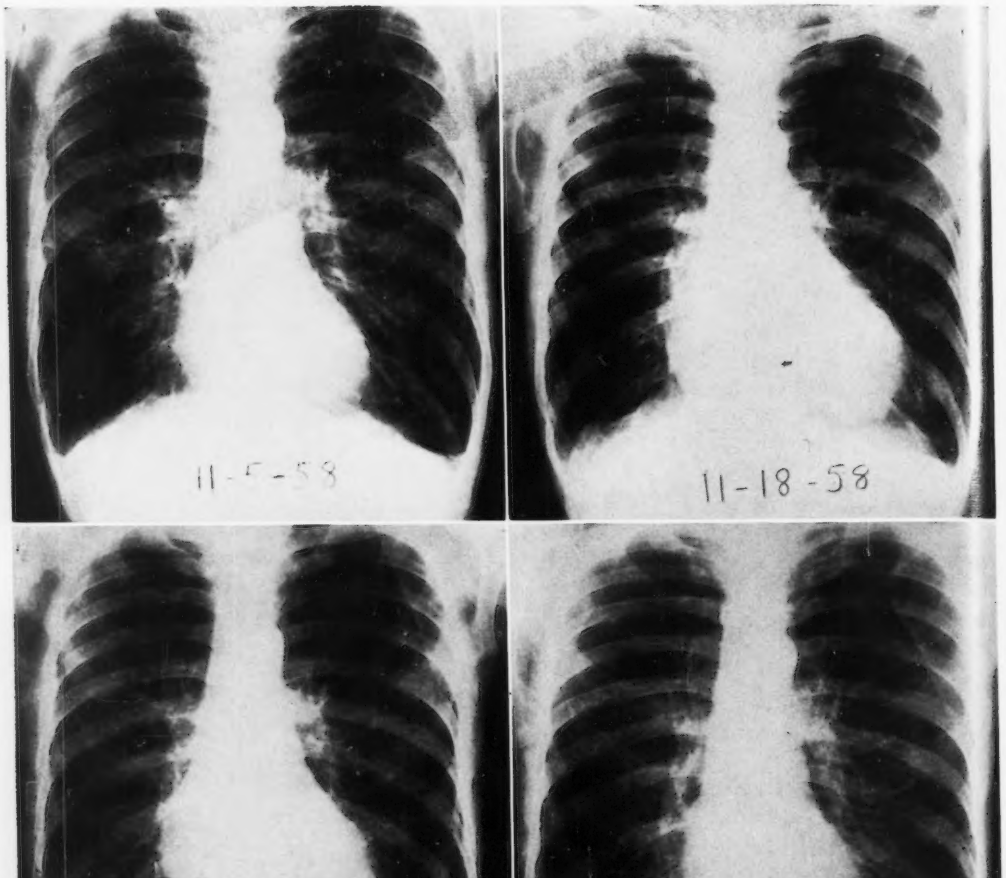

Figure 3

Serial x-ray films of a 57-year-old man (A.F.) with emphysema and cor pulmonale. He was admitted 11/4/58 with a 3-week history of increasing dyspnea and edema (see upper left). He was allowed ambulation in hospital, was given antibiotics and periods on a Bennett respirator but was not digitalized. By 11/18/58 the heart size had greatly increased (upper right) and a pulmonic systolic murmur and a right ventricular gallop appeared. He was digitalized and put on bedrest. Film taken 11/26/58 (lower left) shows a smaller heart and by 12/18/58 when he was no longer in failure, the heart size was normal (lower right). A comparison of the first and last films illustrates that the former actually depicted some cardiomegaly even though the cardiothoracic index was quite normal.

tation, rather than hypertrophy, is the major cause of cardiac enlargement. This observation has pathologic confirmation (fig. 1).

The electrocardiographic findings in cor pulmonale secondary to emphysema are variable, and the record may be quite normal. Right axis deviation, however, is a common finding in emphysematous persons, whether or not they have cardiac disease, and therefore is not an aid in making the cardiac diagnosis. In some patients there may be incomplete or complete right bundle-branch block, and in a relatively modest number the tracing shows the pattern of right ventricular hypertrophy.[14] One should not refrain from making the clinical diagnosis of cor pulmonale because of the presence of left axis deviation, as occasionally a horizontal electrocardiographic position is present. Prolongation of the P-R and Q-T intervals is not encountered. The T waves in the right V leads are sometimes of considerable importance in defining right ventricular disturbances. The T waves may become negative during an acute anoxic period when the right heart enlarges, just as is well known to occur in acute pulmonary hypertension due to pulmonary emboli. Later, with improvement, they may become normal again. Chronic arrhythmias are not a part of the picture but acute anoxic periods even in the absence of heart failure will produce paroxysmal arrhythmias. These disappear with improvement in the anoxic state. Atrial or nodal arrhythmias and even ventricular premature contractions occurring in coupled rhythm may be seen in the phase of acute, recent, or severe cardiorespiratory failure. Indeed, the authors have now seen 7 patients with cor pulmonale due to emphysema who entered the hospital with atrial flutter and this arrhythmia persisted until anoxia was relieved; in some cases this required a number of days. Atrial fibrillation with rapid ventricular rate has also been seen as a result of marked overmedication with vaporized bronchodilators. On the other hand, a long-standing arrhythmia suggests a diagnosis in addition to, or instead of, cor pulmonale.

A word must be added about the rate in normal sinus rhythm in these emphysematous subjects. When they are moderately anoxic, and because of this, they tend to have ventricular rates of 90 to 100. When cardiac failure supervenes, this rate rises even higher and when either severe cardiac or severe respiratory distress is present, sinus rhythm may be extremely rapid; the fatest rate in sinus tachycardia seen by the authors was 215 beats per minute at a time when dyspnea was severe but there was no cardiac abnormality. Overuse of bronchodilator drugs is a common cause of persistent sinus tachycardia. An increase in heart rate should also alert one to an episode of increased anoxia in the emphysematous patient but it should also suggest the possibility of gastrointestinal bleeding. Peptic ulcers occur frequently in the emphysematous subject and may be asymptomatic unless hemorrhage is occurring. If bleeding is ruled out and cardiac failure is absent, an increasing sinus tachycardia will often indicate a serious prognostic sign of advanced pulmonary insufficiency.

Certain tests are of value in confirming the clinical impression of cor pulmonale due to emphysema and in following the course of these subjects. The levels of arterial blood oxygen and arterial carbon dioxide are of primary interest. These respiratory gases give a fairly close estimation of pulmonary insufficiency and, indirectly, of the circulatory changes. The hematocrit level affords direct information about an increased red cell mass and in addition, if elevated, suggests that a hypoxic state has been present for a considerable period of time. Determination of hemoglobin alone is not satisfactory because these red cells although large are hypochromic.[15, 16] Although ultimately one tries to evaluate pulmonary function as completely as possible, measurements of lung volumes and maximal breathing capacity are not always feasible in the state of acute cardiorespiratory failure and must await the subject's recovery.

One might wonder somewhat at the authors' emphasis upon the blood gas determinations in

EMPHYSEMA AND COR PULMONALE

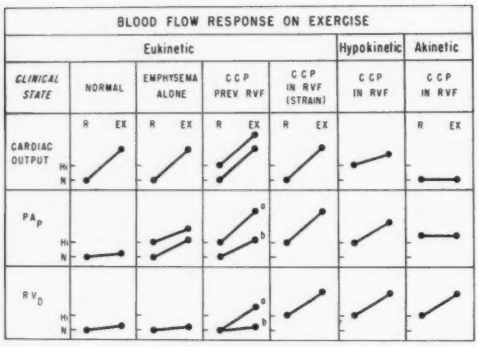

Figure 4

Schema of the response to exercise in emphysema with and without cor pulmonale. Each of the columns is represented by an actual study in an individual patient. CCP, chronic cor pulmonale; RVF, right ventricular failure; Hi, high; N, normal; R, rest; Ex., exercise. With emphysema alone (column 2) the patient can increase his cardiac output in a normal fashion whether or not pulmonary hypertension is present at rest or during this exercise. The rise in blood flow will raise pulmonary artery pressures (PA_p) but if the right ventricle can tolerate this response its diastolic or filling pressure (RV_D) does not exceed normal during the exertion. If the right ventricular filling pressure does rise during exercise (a in column 3) even though blood flow increases normally or is eukinetic, an abnormal cardiac phase is present and physiologically this is probably where cor pulmonale begins. When diastolic ventricular pressure is elevated at rest (column 4), a more advanced cardiac phase exists but, in spite of this, blood flow may still rise adequately. The final phases are shown in columns 5 and 6; the right ventricle can no longer increase its output normally and is hypokinetic or cannot increase it at all above the resting level (akinetic).

judging cardiac function rather than upon a hemodynamic evaluation such as the measurement of peripheral venous pressure. This pressure in the emphysematous chest, as determined at the bedside, is almost invariably too low. This error stems from inaccurate estimation of the atrial level in the thorax and the use of the very low frequency saline manometer.

The disturbances in cardiopulmonary function in cor pulmonale have been thoroughly explored in recent years. The hemodynamic alterations are of great physiologic interest but are not necessary information in making the clinical diagnosis. An understanding of them, however, is very helpful in directing the course of therapy. The cardiac output although it can be elevated is not always so.[12] The elevation in pulmonary artery pressures covers a wide range[12] but very high systolic pressures (over 100 mm. Hg) are not encountered. Indeed, heart failure may be seen when pressures are only moderately increased. Right ventricular diastolic hypertension is the rule in right heart failure. Both the red cell mass and the plasma volume are above normal, the former usually being the more augmented of the two, and hence one often finds an elevated hematocrit value. There is a decrease in all these circulatory measurements on relief of the severe anoxia and heart failure. The level of blood flow, even if it is not above normal, will be lower on recovery as compared to that found in the congestive episode.[12] Although the circulatory abnormalities can be returned to a virtually normal state at rest, one must be aware of the response of the emphysematous subject to exercise. As shown in figure 4, these individuals with emphysema, even if they have never been in heart failure, may develop a considerable pulmonary hypertension on exercise and the arterial saturation may fall below 85 per cent. Those patients who have recovered from failure may also have a normal increase in blood flow but develop considerable pulmonary hypertension and a rise in right ventricular diastolic pressure. A more severe degree of hypoxia will also appear. Thus the 3 stimuli that lead to the reappearance of the congested state may be present during exercise although absent at rest; these stimuli are hypoxia, pulmonary hypertension, and the elevated ventricular diastolic pressure. The last may well be related to salt and water retention.

In these patients with emphysema therapeutic efforts are directed at treatment, not only of the heart failure, but also of the results of pulmonary dysfunction, anoxia, and hypercapnia. Although hypercapnia is a constant finding in those patients with emphy-

sema who develop circulatory complications, there is little evidence to indicate that hypercapnia itself produces them. Carbon dioxide retention, however, is in part responsible for the cerebral symptoms that these patients may display, particularly somnolence and coma.[17, 18] Restlessness, irritability, and paranoia may also be related to abnormalities of gas exchange. The mental status of these subjects in acute cardiorespiratory failure may interfere with therapy. The apprehension, distrust of personnel, and irritability which they display can only be overcome by constant supervision and reassurance by nurse and physician. It is well for the physician to advise the nursing staff that the disagreeable personality these subjects demonstrate is due largely to anoxia and is a major manifestation of their disease.

The importance of bed rest cannot be overemphasized, since it has been shown that the arterial blood oxygen saturation, already low at rest, becomes much lower on exertion and may even fall to 45 per cent in this type of emphysematous subject. Adequate fluid intake and particularly an adequate caloric intake must be almost forced on these weak or somnolent patients.

It is because bronchospasm and bronchopulmonary infections are of paramount importance in the interference with gas exchange that attack on these must be vigorous and, if possible, early. Vaporized bronchodilators used with or without a positive-pressure apparatus are often quite effective in alleviating bronchospasm and mucosal edema. The advantage of the aerosols now in use is that small doses are effective and without side reactions. Three or 4 drops of these preparations diluted with an equal volume of water or saline and given every 4 hours represent a sufficient dosage. It is rare to find a patient who requires more than 7 drops of these drugs per treatment, and the authors have never seen a tolerance develop even after years of usage. When larger amounts are used or intervals between administration are shorter than 4 hours, then tachycardia, tremors, or hyperexcitability follow. Swallowing of even small amounts of these drugs may produce severe epigastric pain. Aminophylline by suppository or slow infusion is often effective in relieving extreme bronchospasm.

The patients who reach the critical state of cor pulmonale with failure almost invariably have infection of the bronchopulmonary tree. The detection of such an infection may rest entirely on symptoms of increasing dyspnea, cough, and change in the quantity or quality of the sputum. There may however be no detectable change in the physical signs in the chest, and x-rays often fail to demonstrate a diffuse lobular pneumonia. Fever and leukocytosis are more often than not absent. Bacteriologic examination of the sputum usually reveals several organisms each of which could be the responsible agent (hemophilus influenzae, pneumococcus, staphylococcus aureus, and gram-negative enteric bacilli) but no one predominates.[19] Because of the difficulty in defining the exact identity of the infective agent (and a viral etiology has not been excluded[20]), these infections are handled much as one would a pneumonia of unknown etiology. The authors have been impressed by the fact that if infection is not attacked directly and intensively, little progress is made in alleviating the cardiopulmonary distress. Antibiotics are used in every case as one cannot ignore what might ordinarily be considered a trivial respiratory infection because the patients do not tolerate well any further encroachments on their pulmonary reserve. The loss of even a small area of functioning lung tissue as a result of infection may be sufficient to precipitate severe pulmonary insufficiency. Clearing of the air passages of secretions and exudates is vital. If the patient can cough he should be regularly encouraged to do so. Not infrequently the sputum is so thick and tenacious that steam inhalation and tracheal suction must be employed. In individuals with marked obstruction due to bronchial plugs bronchoscopy may be life saving. Because of the patient's dyspnea and weakness postural drainage is not feasible. We have not found it necessary to use tracheotomy in our cases, and indeed have been discouraged from its employ-

Table 1

Studies of Arterial Blood Gases as Influenced by the Bennett Respirator or Pneumatic Balance Resuscitator (PBR) in Two Subjects with Emphysema

Patient	State	Arterial Blood O_2 Sat. (%)	Arterial Blood pCO_2 (mm. Hg)	Arterial Blood CO_2 content (vol. %)	Arterial Blood pH
Ni.	On Bennett respirator for 20 min. with 40% O_2	78	—	87.6	—
	Off Bennett respirator for 20 min.	27	—	86.9	—
De.	Before O_2 or respirator therapy	71	69	—	7.35
	1 hour on PBR	84	50	—	7.43
	1 hour off PBR	61	64	—	7.36

ment because of the complications that arise from its presence. Potassium iodide and other expectorants are not very helpful.

Frequently the above measures will improve ventilation sufficiently so that a more effective gas exchange ensues. If this is not the case, oxygen must be supplied. The hazards of administering this gas in high concentration to patients with hypercapnia are well known,[21] and it must be given with assisted respiration by means of a respiratory aid. While it is true that low concentrations of oxygen can be given intermittently unaided by a mechanical respirator without inducing coma, the carbon dioxide tension of the arterial blood rises to precarious levels and unfortunately the patient cannot be persuaded to discontinue this form of oxygen therapy.

A number of respirators are available which can be employed as mechanical aids to ventilation. Although each of these operates in a somewhat different fashion, the ultimate aim of all is to improve alveolar ventilation in such a way that not only is more oxygen conveyed to the alveoli but also carbon dioxide is more effectively eliminated. With some of these aids, ventilation may be improved to such an extent on room air that adequate oxygenation occurs even without the use of high oxygen mixtures in the inspired gas.[22] In the presence of carbon dioxide retention any respirator that depends upon the subject's initiating the cycling mechanism by voluntary inspiration should not be used with concentrations of oxygen higher than 30 to 40 per cent, as one faces the same hazard that occurs in oxygen therapy with unassisted respiration. Under these circumstances, if the patient becomes rapidly saturated with oxygen during the first few breaths, the stimulus to breathing is diminished. Studies of the effects of these respiratory aids on blood gases have confirmed the clinical impression of their value.[21, 22] The rise in arterial saturation and decrease in carbon dioxide tension, however, may be quickly dissipated (table 1) once the respirator is removed from the patient. Prolonged use of the aid, 6 to 20 hours per day, and for periods of no shorter than 45 to 60 minutes on each occasion, will eliminate the fluctuations in levels of anoxia and promote significant lowering of carbon dioxide values.[22] The tank respirators are a boon in handling the semicomatous subject or one whose apprehension precludes covering his face with a mask. Any desired oxygen concentration can be used with these tank respirators. The constant presence of an understanding medical attendant is better than any sedation in securing the cooperation of the sufferer when using any of these respirators.

So far the discussion has centered around the treatment of the pulmonary insufficiency. The specific cardiac therapy of the patient in failure with cor pulmonale is the same as would be used in heart failure due to other forms of heart disease, that is, adequate digitalization, low-salt diet and, when necessary, mercurial diuretics or chlorothiazide. One must remember that one cannot rely solely on the heart rate as an index of full digitalization, as the patients tend to have rapid heart rates, not only because of failure, but also as a result of anoxia. Even when heart failure is not present, they tend to have resting ventricular rates of 90 to 100, and, if digitalis dosage is increased to combat this rapid rate, intoxication may result.

The polycythemic state of these patients is disadvantageous because it promotes an increased venous return to a failing right ventricle and also plays a role in maintaining and exaggerating pulmonary hypertension. In these patients, when the lesser circulation becomes abnormal, an increased blood flow and polycythemia cannot be considered as advantageous homeostatic responses directed toward the satisfaction of tissue oxygen needs in the presence of anoxia, as they are in normal man. Therefore, it is helpful to reduce blood flow and blood volume by means of phlebotomies. Phlebotomies should be performed judiciously, particularly in the acutely ill patient. Indeed, most of the preceding therapies should be instituted prior to blood letting. The volume of venous blood removed may vary from 300 ml. to 500 ml. at each phlebotomy, and the use of a vacuum bottle makes the withdrawal of this viscid fluid fairly easy. Serial measurements of the hematocrit and hemoglobin will indicate the amount of blood that must be removed to return the hematocrit value to 45 to 50 per cent without reducing the hemoglobin below 12 Gm. In this connection, it is important to emphasize that phlebotomies should not be done more often than every 2 or 3 days. Repeated phlebotomies initially may have little effect on the elevated hematocrit value until a considerable volume has been withdrawn.

The dangers of sedation in subjects with cardiorespiratory failure due to emphysema are well known. Since every effort is being made to improve ventilation and to clear the respiratory passages of secretions in the presence of a poor cough mechanism, it is obvious that the use of morphine, meperidine, and codeine are contraindicated. Barbiturates and tranquillizers have also proved deleterious. If sedation is absolutely necessary, chloral hydrate can be administered. The chest pain ascribed by some to pulmonary hypertension has not been encountered in our patients. The low chest and high epigastric pain, we have noted, was the consequence of either chronic cough or peptic ulcer, so that analgesics mentioned above have not been required. A word of warning must be added here about the use of nitroglycerin in these anoxic subjects. This drug, a powerful peripheral vasodilator, when coupled with another systemic vasodilator such as hypoxia, can produce profound peripheral vascular collapse.

The use of steroids has been advised[21] but in our experience the complications, namely gastrointestinal bleeding and fluid retention, following therefrom have been more serious than the benefits to pulmonary function said to accrue.

If pursued unremittingly, all these measures will result in improved pulmonary function, reduction in and even abolition of pulmonary hypertension at rest, and relief of right heart failure. In fact, it has been our experience in recent years that the problem of heart failure per se can almost invariably be resolved in these subjects. The pulmonary insufficiency, however, remains as the important and sometimes fatal disability. When heart failure persists despite the measures discussed above, one should reconsider the diagnosis, as it is unlikely that emphysema alone is the primary cause of the difficulties.

Once the patient has recovered from the acute episode of cardiopulmonary insufficiency, all efforts are directed at maintaining him free of circulatory complications and in as optimal a state of pulmonary function as is possible with modern methods. These patients should be followed regularly and at frequent intervals, even when they are doing well, not only for appraisal by the usual clinical means, but also for evaluation by certain simple physiologic measurements.

One can obtain essential information concerning pulmonary function from analysis of the arterial blood for its oxygen saturation and the carbon dioxide content, associated, if possible, with a determination of the arterial pH, so that carbon dioxide tension can also be calculated. If the emphysematous patient with cor pulmonale is well controlled, there are only minor fluctuations in arterial blood oxygen saturation and carbon dioxide content. The frequency with which these determinations need to be made depends upon many

factors, and in our experience may vary from 1 to 3 months, depending upon the severity of the individual patient's disease and the occurrence of complications. The oxygen saturation may vary as much as 10 per cent on repeated monthly samplings but is usually found to be above 80 to 85 per cent if the patient is doing well; the carbon dioxide tension generally lies in the range of 45 to 55 mm. Hg when the patient is well controlled. It is necessary to obtain such data because it is often difficult to demonstrate changes in the patient's condition by clinical examination alone. The acute respiratory infection is apparent to patient and physician alike, but there may be a clinically imperceptible and gradual change that is uncovered only by serial laboratory determinations. The cause of this gradual decline in pulmonary function is not always clearly demonstrable, but frequently it is reversible by an intensification of the therapeutic pulmonary regime.

Advice concerning the physical activities to be engaged in by these patients must be given on an individual basis. The persisting dyspnea and fatigue limit exertion but the patient should be encouraged to operate at least up to that limit. Since the arterial saturation may fall considerably on exercise in some of these cases, sudden or strenuous exertion is best avoided. Airplane travel may be hazardous unless the cabin is adequately pressurized.

Vaporized bronchodilators are used systemically 3 or 4 times a day. The inhalations should be taken until the prescribed volume of fluid has been dispensed; this generally requires 10 to 15 minutes. A few puffs of the medication are inadequate. Those fortunate individuals who possess a respiratory aid and use it regularly 2 to 4 hours every day have been maintained in a far better state of alveolar ventilation than prior to its use. Smoking must be discouraged, and on numerous occasions renunciation of this habit has made a striking change in the patient's clinical state.

The course of the patient with emphysema is in large measure determined by the frequency of bronchopulmonary infections. These infections may not only precipitate acute cardiopulmonary failure but often, because of their poor resolution, destroy areas of functioning lung tissue. Obviously intensive treatment by antibiotics of even a seemingly minor infection is mandatory. It is not necessary to use a different antibiotic at the time of each new infective episode, and if one drug is repeatedly successful there seems little reason to try a different agent. Whether or not prophylactic therapy will abolish some of these recurrent infections is not yet settled,[20] nor is the relative value of continuous or intermittent programs or the effectiveness of various drugs. A preliminary study conducted at Bellevue Hospital by Davis and associates[20] indicates that although prophylaxis changed the flora in the sputum and even reduced the number of lower respiratory tract infections in the treated group, the infection rate was still so high in this group that the effect of the drugs was considered minimal.

If repeated measurements of the hematocrit level show an increasing red cell mass, phlebotomies are performed as indicated. Obviously the hematocrit level may be measured from the arterial blood sample drawn for blood gas analysis, but venous blood, if properly drawn (that is, without use of tourniquets) will suffice. In the patient who must be repeatedly phlebotomized—and this may vary from bimonthly to biennially—iron-containing foods should not be withheld, as this will not depress red cell formation effectively and serves only to increase the hypochromia.

The patients who have been in cardiac failure are maintained on digitalis preparations. This attitude is dictated by the fact that on numerous occasions patients who had this drug stopped for one reason or another have returned with evidences of heart failure. The physiologic reason for this may depend on the fact that even though these subjects may have normal pulmonary artery pressures at rest they will develop pulmonary hypertension and anoxia on exertion. However, it is not our custom to institute digitalization in patients with emphysema who have never shown any evidence of heart failure. One must always remember that cough and dys-

pnea are symptoms of pulmonary and not cardiac dysfunction in these patients, and hence are not indications for digitalis or mercurial diuretics in the absence of right heart failure.

Following the progress of the emphysema by means of serial chest x-ray films is not often helpful except in the diagnosis of complicating pulmonary infections. Repeated measurements of heart size, however, are useful, since it has been shown that the heart diminishes in size once heart failure is relieved. Similarly, an increase in heart size in these patients suggests the onset of heart failure even though the clinical manifestations of peripheral congestion may not yet be present.

Diamox is another useful adjunct. It not only acts as a diuretic but it may also promote elimination of carbon dioxide. Inasmuch as this drug produces a metabolic acidosis, it should be discontinued in the patient with acute respiratory insufficiency because of the danger of increasing acidosis. However, in those patients who are improving as a result of the other measures mentioned but who nonetheless continue to show hypercapnia it is often successful in lowering carbon dioxide tension.

Silicosis

The appearance of cardiac complications secondary to pneumoconiosis has been noted predominantly in silicotic and anthracosilicotic subjects. Silicosis can be divided into "simple" (or nodular) silicosis and "complicated" silicosis (massive fibrosis or pseudotumoral form). This subdivision is useful when cardiovascular complications are considered. Right heart enlargement is infrequently seen with simple pneumoconiosis[23] unless there is coexisting emphysema.[4, 5] However cor pulmonale is a frequent accompaniment of complicated silicosis.[5, 23] Lavenne[4] found that 40 per cent of miners with anthracosilicosis have right ventricular hypertrophy on autopsy. Furthermore the statistics he reported from Gough's service, based on 358 autopsies of Welsh coalminers with pneumoconiosis, indicate that right heart failure was a more frequent cause of death (23.7 per cent) than tuberculosis (13.7 per cent). Since therapy of tuberculosis has made such strides in recent years, it is obvious that cor pulmonale will soon far outstrip tuberculosis as the major complication in silicosis.

The pathogenesis of right heart enlargement, with or without failure, secondary to silicosis is still being investigated and therefore no definitive outline of this phenomenon can be given. Physiologic studies are underway at present[24] that should elucidate the problem in the same way as has been done in the pathogenesis of cor pulmonale due to emphysema alone. It has been assumed that in silicosis, as in other lung diseases producing cor pulmonale, pulmonary artery hypertension represents the major physiologic cause for the right heart enlargement and eventual failure. The inciting mechanisms for this hypertension may include not only a pathologic encroachment on, and destruction of, the pulmonary vasculature by the fibrosis (particularly the lesions seen in complicated silicosis[25, 26]) but also the physiologic effects of anoxia. The solution of the problem is greatly complicated by the fact that silicosis is very frequently accompanied by pulmonary emphysema. This is not only the perifocal type involving the lung tissue surrounding the silicotic and anthracotic nodules, but also the bronchitic type, which in itself is the commonest cause of cor pulmonale. Bullous areas and pulmonary as well as bronchiolar infections, all of which may impair respiratory gas exchange, are also frequent complications. Lavenne,[4] whose exhaustive monograph is our most adequate appraisal of cor pulmonale due to pneumoconiosis to date, reports on the detailed pathologic findings in 100 cases dying in right heart failure. There were 79 cases of complicated (massive fibrosis) silicosis, of whom all but 5 had obstructive emphysema. There were 16 cases of simple silicosis, all of whom had considerable obstructive as well as perifocal emphysema; and the remaining 5 cases had advanced obstructive emphysema as their main lesion associated with a few coal nodules and a little perifocal emphysema. Thus, of this series of 100 cases with fatal

right heart failure due to pneumoconiosis, 95 had obstructive emphysema. Finally, in a small series of silicotic patients studied by us[15] obstructive emphysema always played a significant role in the pathophysiology whenever cor pulmonale was present.

These observations raise a very important point: does cor pulmonale occur in the silicotic subject who has no emphysema? The answer is not definitely known, but the implications are that it must be rare.[24] If this is so, the circulatory complications in silicosis may be greatly if not entirely the result of the disturbances secondary to the alveolar hypoventilation of emphysema.

It may well be that the vascular lesions described[25, 26] in the conglomerate (pseudotumoral) complicated forms of silicosis are such as to produce this fixed type of pulmonary hypertension but this has not been shown as yet. Furthermore, Lavenne[4] has noted the relief of right heart failure in these patients following treatment, suggesting that there may be some measure of reversibility even in such a severely altered pulmonary vasculature. He observed that these bouts of failure almost always followed acute respiratory infections and that the silicosis in these cases was accompanied by emphysema, so that anoxia again may be the more important mechanism.

It is probable that in the silicotic subject both mechanisms for the production of cor pulmonale—anatomic lesions and anoxia—coexist in varying proportions, and their importance in any single case depends on the relative extent of the vascular lesions and the obstructive emphysema.

From what has been said it seems apparent that one diagnoses the presence of cor pulmonale in the silicotic subject in much the same manner as one does in the emphysematous patient.[27] Moreover, the success of therapy will depend on the ability to alleviate anoxia. The therapies described for the management of emphysema are applicable here.

Neuromuscular Diseases

Central nervous system lesions that lead to depression of the respiratory center as well as the lesions of poliomyelitis, Guillain-Barré disease, myotonic dystrophy,[28] and other myopathic diseases—may result in alveolar hypoventilation and cor pulmonale because the muscles of respiration are not properly stimulated or are themselves too weak to perform their function adequately. The lungs themselves are normal. Treatment consists almost exclusively of combating intercurrent pulmonary infection and maintaining adequate ventilation by use of respirators. The prognosis in these circumstances rests with the progress of the primary disease although the heart failure may be reversible.

Structural Deformities of the Chest Cage

Kyphoscoliosis[2] and surgical alterations of the chest cage may disturb the mechanics of breathing to such a severe degree that hypoventilation with anoxia and hypercapnia appear and circulatory disturbances follow. This however is a rare eventuality; it is much commoner for these subjects with chest deformity to develop the respiratory gas and circulatory alterations because of either recurrent bronchopulmonary infections or an accompanying emphysema. The treatment again revolves around provision of adequate gas exchange by means of respirators and attack upon the infections. Both positive-pressure and tank respirators have been used successfully in these patients. Vaporized bronchodilator drugs are not always effective and, if this is demonstrated, it is wise to discontinue them. Obviously it may be extremely difficult to delineate heart size in such chests.

Obesity

In certain fat people circulatory disturbances can appear in association with alveolar hypoventilation. Although the ultimate mechanisms are not well understood[3] it is agreed that the excess fat plays a large role. This is best demonstrated by the fact that weight loss initiates a reversal of the syndrome. The lungs themselves appear normal but there may be increased need for gas exchange as well as increased resistance to ventilation as a result of the masses of fat. Whether, in addition, there must also exist a disturbance in

espiratory control centers in the central nervous system remains to be proved.

Cystic Fibrosis of the Pancreas

In this disease of children, the bronchial and bronchiolar obstruction due to viscid secretions and infections produces a picture similar to that seen in the adult with obstructive or bronchitic emphysema, and therapy is much the same in both groups. Efforts to thin the secretion by enzymatic agents may be successful.

Bronchiolitis

This other common cause of cor pulmonale in children in the western hemisphere is usually an acute respiratory illness without antecedent symptomatology. It is a diffuse inflammatory reaction associated with intense bronchospasm which can rapidly initiate alveolar hypoventilation. With treatment of bronchospasm and infection, the patient may have no further cardiopulmonary dysfunction.

Diseases That Produce Cor Pulmonale by Reduction of the Pulmonary Vascular Bed

This type of cor pulmonale, in contrast to that seen with alveolar hypoventilation, develops in the late stages of the diseases that cause it and is characterized by pulmonary hypertension, which so far has appeared to be irreversible.

Multiple Pulmonary Emboli

Although this is considered a rare cause of cor pulmonale, cases are being encountered in increasing number as a result of more careful attention to diagnosis. The site of origin of the emboli is usually in the pelvic or leg veins. There is a higher incidence in women than in men. In women one almost always finds a history of pregnancy, either at term or interrupted by abortion, or pelvic inflammatory disease prior to the onset of symptoms. In men the prostatic plexus or leg veins are noted as the source of the emboli. Embolization may be recurrent over several years with resultant obliteration or narrowing of many of the smaller vessels. The chronicity is indicated by pathologic specimens in which evidences of sclerosis, recanalization, and recent emboli can be found in the same microscopic section. These vascular occlusions seldom cause pulmonary infarcts that can be detected clinically. In some instances it may be impossible to distinguish such lesions from those due to the pulmonary arteritides with intravascular thromboses unless the lungs are only a part of a generalized vascular disease. In these patients with longstanding pulmonary hypertension, right ventricular hypertrophy is often quite marked in contrast to subjects with emphysema, in whom only dilatation or minor hypertrophy may be seen.

The onset of this illness may be difficult to determine. Complaints of sudden bouts of dyspnea occasionally associated with chest pain and sometimes accompanied by minor hemoptysis may be elicited for several years before evidences of right heart enlargement appear. The source of the emboli may not be readily apparent. Frequently the x-ray and electrocardiogram reveal no abnormalities during the early phase of the illness. Because of the paucity of objective findings early in the disease, these patients are often designated as psychoneurotics, especially since weakness and fatigue are prominent symptoms at this point. Ultimately one is confronted with a dyspneic patient with large pulmonary arteries and right heart enlargement in whom cyanosis may not be marked. The electrocardiogram at first indicates right ventricular change by inversion of the right precordial T waves but eventually most of these individuals show the characteristics of right ventricular hypertrophy. When right heart failure appears it is usually intractable and marks the onset of the phase of rapid deterioration. The ensiform gallop is a reliable physical sign of heart failure. The total course of this disease may last 5 to 10 years, although, in general, heart failure appears late. Except for treatment of heart failure, therapy is almost nonexistent, since the illness is rarely diagnosed until it is far advanced. Hence the efficacy of anticoagulants is not known. If the diagnosis is made prior to extensive destruction of the bed, ligation of the offending veins or even the inferior vena cava can be life saving. Drug

therapy directed at the hypertension, so far has been unsuccessful.

Tests of cardiopulmonary function may help to confirm the clinical diagnosis. There are marked hyperventilation and a low carbon dioxide tension of the arterial blood. At the stage of heart failure there is usually arterial oxygen unsaturation that may be as low as 80 per cent at rest, falling markedly on exercise. The unsaturation probably springs from a combination of changes, namely, a reduction in the diffusing surface of the pulmonary vascular bed and the development of intravascular pulmonary shunts. Some increase in hematocrit and hemoglobin may be present. These patients may have the highest pulmonary artery pressures found in cor pulmonale and their cardiac output is usually low. The hypertension is probably the major determinant of the cardiac involvement since the anoxia is seldom severe and blood volume is only slightly abnormal.

Syndrome of Alveolar-Capillary Block

Under this general heading come the diseases that produce lesions in the alveolar-capillary membrane and that are characterized by difficulty of oxygen diffusion.[29, 30] These include berylliosis, Boeck's sarcoid, scleroderma, and certain granulomatous lesions and reticular fibroses of undetermined etiology. These patients offer some interesting contrasts to those patients with cor pulmonale due to emphysema. The respiratory illness is usually short, unremitting, progressive and associated with an extraordinary tachypnea and little cyanosis. There is no obstructive breathing, and the lungs may be clear on physical examination or may show widespread rales. In some of these patients death from the rapidly worsening pulmonary insufficiency may occur before evidences of cardiac insufficiency appear. In those who do develop heart failure, it is irreversible and very often a terminal event. This is quite different from patients with emphysema in whom heart failure may occur at any time in the course of the disease when severe acute anoxia supervenes and in whom heart failure may be completely reversible and preventable. It is of interest that the authors have heard a basal diastolic murmur of pulmonic incompetence only in patients with irreversible pulmonary hypertension, i.e., those with fibrosis or embolization. The findings on chest x-ray depend of course on the nature of the pulmonary disease. If the hilar and paramediastinal areas are markedly fibrotic, the definition of cardiomegaly may be difficult. The electrocardiographic alterations are the same as those seen in cases of multiple emboli and are the expression of progressive right heart hypertrophy. In these subjects with difficulty in diffusion due to thickness of the alveolar capillary membrane or a reduction in its area, studies of cardiopulmonary function will indicate the defect. The resting arterial saturation is only slightly, or at most moderately, decreased, and carbon dioxide levels are not elevated and may even be diminished when hyperventilation is severe. Pulmonary hypertension and right heart enlargement may be present before even moderate anoxia appears at rest, therefore it seems likely that anatomic lesions are primarily responsible for the developments of cardiac complications. Of course as the lung disease progresses and severe anoxia occurs, either at the end stage or because of a complicating pulmonary infection or focal emphysema, its effects are superimposed. Heart failure is usually not seen until severe anoxia is present at rest. In contrast to patients with multiple emboli, these subjects have a high resting cardiac output but it is not on a hypervolemic basis, as polycythemia occurs uncommonly, except in the terminal phase. The exact stimulus for this hyperkinetic flow is unknown.

It is obvious then that therapy in cardiac failure due to chronic pulmonary fibrosis or pulmonary granulomas, with their irreversible pulmonary hypertension, cannot be expected to be as beneficial or successful as in cor pulmonale due to emphysema. Nevertheless digitalis may reverse evidences of failure and should be administered and maintained. Polycythemia is not a frequent com-

p cation but if present should be relieved. A tention to pulmonary infection is of great i portance. The use of oxygen by the usual c nical means is satisfactory and is to be encouraged as long as there is no complicating p lmonary emphysema with its dangerous h percapnia.

There is as yet little direct therapy for the p imary pulmonary disease in these patients. I is reasonable to suggest that until better c culatory studies are available in all forms o pulmonary fibrosis physical exertion should b curtailed, as it is only by maintaining as l w a level of pulmonary artery pressures as possible that right heart strain can be minimized. In the granulomas the use of steroids has offered some hope of limiting the cellular proliferation causing the syndrome of alveolar-capillary block. However, it is not always possible to control the degree of pulmonary fibrosis that results from hormonal treatment.

Chronic Pulmonary Diseases Seen in Association with Certain Forms of Organic Heart Disease

Chronic pulmonary diseases capable of producing circulatory abnormalities may occur along with organic heart disease. Usually, however, when these two disease entities coexist the patient does not present with the classical picture of cor pulmonale. Even if the nature of the pulmonary disease (and this is most frequently some form of emphysema) is identified by studies of pulmonary function, it is probably advisable to avoid the diagnosis of cor pulmonale. The reasons for this are the following: (1) the clinical course and prognosis are almost always dominated by the organic heart disease; (2) therapy must take both diseases into consideration and the results will depend upon the stage of the organic heart disease; (3) disturbances in gas exchange in these combined states are rarely as severe as in patients with uncomplicated cor pulmonale. Since anoxia is seldom marked (below 80 to 85 per cent), one is uncertain if the circulatory complications produced by anoxia are present. These patients with organic heart disease develop evidences of congestive failure with minor degrees of unsaturation. Indeed the levels of anoxia at which failure is seen are those one would be gratified to be able to maintain in patients with uncomplicated cor pulmonale. On the other hand, this level of unsaturation probably acts in a deleterious fashion upon the primarily disturbed ventricular myocardium. The fact that the patient with cor pulmonale develops heart failure at much lower levels of saturation than does the one with organic heart disease suggests that in the former the integrity of the myocardium has been fairly well preserved. One does not usually see marked hypercapnia in spite of severe emphysema in the presence of organic heart disease. This probably stems from the hyperventilation these individuals demonstrate when in the congestive state.

The presence of an enlarged left ventricle or left atrium precludes making the solitary diagnosis of cor pulmonale. Conversely, there is practically no form of acquired organic heart disease that results in isolated enlargement of the right heart and pulmonary arteries. Pure mitral stenosis, if it is hemodynamically important enough to produce right cardiomegaly, is usually accompanied by some left atrial abnormality.

A few comments should be added concerning therapy in patients with organic heart disease and chronic pulmonary disease. The minimal degree of carbon dioxide retention in the majority of these cases is reassuring in considering oxygen therapy and permits the use of high oxygen concentrations without risk of narcosis. The presence of arteriosclerotic heart disease warrants caution in the use of sympathomimetic bronchodilators as tachycardia and angina may be complications of these drugs. Aminophylline administered by suppository or infusion is often a satisfactory substitute. If bronchospasm and bronchial infection are severe, one should not hesitate to use mechanical respirators. The type of respirator that requires the dyspneic subject to initiate the inspiratory cycle may prove intolerable in those with primary heart

disease. If one supplies an apparatus with a very low opening or inspiratory pressure, as well as a very high rate of instantaneous flow, the respirator is acceptable. The tank type of respirator can also be used.

Summary and Conclusions

A number of different forms of pulmonary dysfunction are now recognized as causing cor pulmonale, and the disease processes acting as etiologic agents are numerous and variable. There are however only 2 basic pathophysiologic mechanisms that compromise the heart, and upon knowledge of these depends successful therapy.

Summario e Conclusiones in Interlingua

Es recognoscite in nostre dies que un numero de differente formas de dysfunction pulmonar pote esser le causa de corde pulmonal e que le processos pathologic fungente como agentes etiologic es numerose e variabile. Tamen, il existe solmente 2 mechanismos patho-physiologic fundamental que affice le corde, e le cognoscentia de istos es le pre-condition de successo therapeutic.

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Concluding Articles of Symposium on Congestive Heart Failure To Appear in March 1960 Issue

Pediatric Aspects of Congestive Heart Failure. *Alexander S. Nadas* and *Anna J. Hauck*

Congestive Phenomena Occurring in Pregnant Women with Heart Disease. *C. Sidney Burwell* and *James Metcalfe*

Unusual Causes of Heart Failure. *Howard B. Burchell*

Rehabilitation in Congestive Heart Failure. *Howard A. Rusk* and *Menard M. Gertler*

CLINICAL PROGRESS

The Correlation Between the Electrocardiographic Patterns of Ventricular Hypertrophy and the Anatomic Findings

By RALPH C. SCOTT, M.D.

THE correlation of the electrocardiographic patterns of ventricular hypertrophy with the anatomic findings offers a firm basis for an appraisal of the accuracy of electrocardiographic criteria.

The attempt to make such a correlation, if it is to have value, however, must be based upon certain careful considerations. The anatomic evidence of ventricular enlargement must be critically approached. Separating the right and left ventricles and weighing and measuring each is the ideal manner of determining individual chamber hypertrophy. This was the method employed (with slight variation) by Müller,[1] Lewis,[2] Herrmann and Wilson,[3] Jones,[4] and Stofer and Hiratzka.[5] However, this is a tedious process, and accurate division and apportionment of the interventricular septum to the appropriate ventricle frequently poses a difficult problem. An alternative and easier method, advocated by Fulton and associates[6] and employed by Grant,[7] involves cutting the right ventricle free at its junction with the interventricular septum and considering the latter a part of the left ventricle. The weights of the normal ventricles as determined by these investigators are listed in table 1. The normal left ventricular/right ventricular weight ratios are also given.

The anatomic division of the septum into right and left ventricular components in the past has been a source of difficulty and inaccuracy.[2-4, 6] More recent studies[8-10] have shown that the right and left septal masses can be separated. It has also been shown that in the upper two thirds of the septum the left septal mass constitutes 70 to 80 per cent of the total septal mass.[10] In left ventricular hypertrophy (LVH) the left septal mass forms more than 80 per cent of the total and in right ventricular hypertrophy (RVH) the right septal mass may comprise 50 per cent or more of the septal weight.[10]

The majority of studies dealing with electrocardiographic and pathologic correlations, however, have not included such careful separation of the ventricular muscle mass. Instead, they have been based upon careful measurement of the thickness of the free wall of the right and left ventricles or the determination of the total heart weight. The normal total heart weight varies with the sex, body length, and weight[11] and ranges roughly from 200 to 400 Gm.[11, 12] Most workers consider that in order to diagnose RVH in an adult the greatest thickness of the right ventricle must be 5 mm. or more, and to diagnose LVH the greatest thickness of the left ventricle must be 13 (or 14) mm. or more. Care must be taken not to include the papillary muscles in this measurement. In studies from our laboratory the additional stipulation was made that the total heart weight exceed one standard deviation above the mean of normal predicted for the body length according to Zeek's criteria.[11] It is true that some cases of anatomic RVH may not be included by insisting on this last criterion, since, as has been pointed out by White,[12] Thomas and James,[13] and Fulton and associates,[6] the right ventricular

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Table 1

Normal Ventricular Weights

Author Year	No. of cases	RV Gm. Range	RV Gm. Av.	LV Gm. Range	LV Gm. Av.	Septum Gm. Range	Septum Gm. Av.	Total ventricular weight Gm. Range	Total ventricular weight Gm. Av.	LV/RV Range	LV/RV Av.
Lewis 1914[2]	11*	35-60	44	54-117	81	14-30	23	104-108	149	1.50-2.06	1.83
	12†	28-70	47	60-112	82	13-46	27	105-221	156	1.57-2.18	1.79
Herrmann and Wilson 1922[3]	16		44		77		21		141	1.46-2.14	1.74
Fulton et al. 1952[6]	43	23-68	46	48-123	86	17-61	39	88-235	171		1.9
Stofer and Hiratzka 1952[5]	82 (54 males) (28 females)		61.87		119.78				307.43		
			±11.81		± 13.88				± 21.65		1.9
			49.75		96.39				244.61		
			± 9.80		± 18.40				± 23.05		
Jones 1953[4]	85		33		66		66		165	1.36-2.43	1.92
											2.0

*"Cancer controls."

†"Controls."

LV: Left ventricle; RV: Right ventricle; LV/RV: Left ventricular/right ventricular weight ratio; LVH: Left ventricular hypertrophy; RVH: Right ventricular hypertrophy.

LV/RV above 2.20 indicates left ventricular preponderance.[3]

LV/RV below 1.50 indicates right ventricular preponderance.[3]

LV+S/RV ranges from 2.3 - 3.3 normally; in isolated RVH this ratio always less than 2.[6]

Free wall RV of 80 Gm. or more indicates RVH;[6] right ventricular preponderance may occur in small hearts with right ventricular weights less than 80 Gm.[13]

Free wall of LV+S normally less than 190 Gm.;[6] when 250 Gm. or more indicates LVH.[6]

muscle mass may be increased in some cases without the total heart weight being abnormal.

Many sets of electrocardiographic criteria have been developed over the years for the diagnosis of RVH, LVH, and combined ventricular hypertrophy (CVH). These have been largely empirical and some have proved unreliable. The ideal electrocardiographic criteria for ventricular hypertrophy would indicate all cases of hypertrophied right or left ventricles and would not so diagnose any normal cases. This is not possible with presently available criteria.

Résumé of Electrocardiographic-Pathologic Correlation Studies

Left Ventricular Hypertrophy

The electrocardiographic diagnosis of LVH is one of the easiest and one of the most important diagnoses to be made from the clinical electrocardiogram. The many criteria that have been proposed[14-25] can be summarized as being based upon abnormal left axis deviation, high voltage in left precordial leads, delayed left ventricular activation time, or ST-segment and T-wave abnormalities.

Noth, Myers, and Klein[21] analyzed the precordial electrocardiogram in 84 pathologically proved cases of LVH, and in 52 cases in which the heart was normal at autopsy. They found that the normal electrocardiogram and the LVH pattern could not be differentiated from the amplitude of the R waves in V_5 and V_6 alone. Of the 84 cases of LVH, 34 (41 per cent) showed a Q-R duration of 0.05 second or longer or an R duration of 0.04 second or longer. The average cardiac weight in this group was 610 Gm. Eight (10 per cent) showed borderline values (Q-R of 0.048 to 0.049 or R of 0.038 to 0.039 second) and the cardiac weight averaged 569 Gm. Forty-two

cases (50 per cent) showed normal Q-R or R duration and had an average cardiac weight of 536 Gm. These workers found a general trend toward increasing duration of Q-R or R with increasing heart weight but many individual exceptions were encountered. Of interest was their observation that 4 cases of anatomic LVH showed normal electrocardiograms.

Levine and Phillips[26] studied 38 cases that satisfied the electrocardiographic criteria of Wilson[20] for LVH.

At autopsy all cases showed anatomic LVH. Scott and associates[27] collected 100 cases of autopsy-proved isolated LVH in adults. Eight sets of currently employed electrocardiographic criteria[18-25] for the diagnosis of LVH were then subjected to analysis in these 100 cases. The criteria of Wilson[20] and of Sokolow[22] were found to give the highest number of positive diagnoses. One or more of Wilson's criteria were present in 81 per cent of cases. However, it was observed that if a minimum of 2 of these criteria were required, only 53 per cent of the cases showed positive diagnoses. One or more of Sokolow's criteria were found in 85 per cent of cases. Similarly, if 2 or more of these criteria were required, the number of positive diagnoses diminished to 64 per cent.

The incidence of the various types of electrocardiographic criteria encountered in this series of 100 cases of isolated LVH is interesting: ST-segment or T-wave abnormalities (67 per cent); prolonged Q-T (48 per cent); high voltage (29 per cent); delayed onset of the intrinsicoid deflection, or prolonged duration of the QRS (28 per cent); ratios derived from these findings (57 per cent). The horizontal heart position was encountered in 36 per cent while abnormal left axis deviation (−30° or more) occurred in 21 per cent.

There were 2 cases in which early LVH was missed by all criteria. A significant association was found between increasing heart weight and increasing accuracy of diagnosis by Sokolow's criteria. It was emphasized that this study tested only the positive findings according to the various criteria in cases of proved LVH. It did not test the specificity o these criteria, that is, the occurrence of fals positive diagnoses.

Chou and co-workers[28] attempted to evalu ate the specificity of these same electrocardio graphic criteria in the diagnosis of LVH. Th autopsy findings of 100 cases diagnosed a LVH by the electrocardiogram were analyze with regard to anatomic ventricular hype trophy. The electrocardiographic diagnose were made with the combined criteria previ ously reported.[27] In all cases the tracings wer taken within 3 months before death. No case of myocardial infarction were included. There were 44 cases with isolated LVH, 45 with CVH, 1 with isolated RVH, 1 with no ventricular hypertrophy, and 9 with questionable hypertrophy. The 9 cases with questionable hypertrophy included 3 with increased heart weight but normal ventricular measurements and 6 cases with normal heart weight but increased ventricular measurements. A review of the electrocardiographic findings in the positive, false positive, and questionable groups failed to reveal any distinguishing features among the various criteria.

Selzer and associates[29] have also recently approached the problem of the reliability of the electrocardiographic diagnosis of LVH. They studied 108 tracings that demonstrated the pattern of LVH by the same electrocardiographic criteria[18-25] employed in our earlier study[27] in which autopsy findings were available. These workers relied upon total heart weight in the assessment of anatomic LVH, considering abnormally heavy those hearts weighing more than 25 Gm. above the upper limit of normal according to Zeek's criteria.[11] Some of the hearts in this study, however, also showed anatomic evidence of RVH, based upon an LV/RV wall thickness ratio of 3 to 1 or less. They encountered 75 cases in which the electrocardiographic diagnosis of LVH was confirmed pathologically, 16 cases in which the hearts were of borderline hypertrophy, and 17 in which there was no anatomic LVH. In none of the 17 cases with normal heart weights was there demonstrable cause for cardiac hypertrophy. The majority of pa

ients in this group died of malignant disease nd showed considerable emaciation. They valuated the frequency of the 3 main classes f electrocardiographic criteria: high voltage, prolonged ventricular activation time, and ST-T alterations. In their 75 cases of autopsy-proved LVH, these criteria were encountered n 71, 40, and 65 instances respectively. Of particular interest were the observations in he 17 cases without LVH in which these criteria were found 16, 6, and 7 times respectively. Thus, any of these electrocardiographic criteria may occur in the absence of anatomic LVH. Nineteen of the 75 proved cases of LVH exhibited a horizontal heart position. There was only a slight preponderance of this position in the heavier hearts than in the lighter and false-positive cases. Eleven of their 75 cases of proved LVH also had anatomic RVH, yet displayed LVH in the electrocardiogram. These authors suggest that CVH may tend to rotate the mean electrical axis to a more vertical position. While high voltage in the precordial leads was the most sensitive criterion, being present in most cases in the series, it was also most frequently responsible for a false diagnosis of LVH. A somewhat surprising finding was their observation that the prolonged ventricular activation time was the least reliable sign. Also of interest was the fact that 6 of the 40 heaviest hearts in the series showed normal ST-T portions. These workers found that electrocardiograms displaying more than one criterion were more reliable in the diagnosis of LVH. While these authors considered ST-segment depression and T-wave inversion (in leads exhibiting high upright QRS complexes) not specific enough to constitute the sole basis for a diagnosis of LVH, yet the addition of this criterion to the criteria of high voltage and delayed ventricular activation time constituted the most specific combination for the diagnosis of LVH.

Selzer and co-workers[30] have also investigated the problem of the false-negative electrocardiographic diagnosis of LVH. They reviewed the electrocardiograms from nearly 300 patients whose hearts at autopsy weighed over 400 Gm. These cases were divided pathologically into pure LVH, pure RVH, and CVH. The actual number of cases in each category was not stated. Cases with myocardial infarction, fibrosis, or bundle-branch block were *not* excluded. They stated that by means of "any acceptable" electrocardiographic criterion the diagnosis of LVH was made in 45 per cent of patients displaying LVH or CVH at autopsy. In 32 per cent the diagnosis of LVH was obscured by the pattern of myocardial infarction or nonspecific ST-T abnormalities and in 8 per cent the diagnosis of LVH was obscured by bundle-branch block. In 15 per cent of the group the electrocardiograms were normal or near normal, despite appreciable LVH at autopsy. These constituted true false-negative diagnoses.

Grant[31] assessed the role of LVH in the production of left axis deviation (LAD) in an electrocardiographic-pathologic correlation study that included 672 cases. He studied 73 cases of anatomic LVH, employing the criteria of hearts weighing over 500 Gm., together with an increase in thickness of the left ventricular wall. These, of course, are rather extreme criteria and would exclude cases of less marked LVH. He found 35 of these 73 cases to exhibit LAD, 35 with a normal axis, and 3 with a vertical axis. He further observed that the development of LAD is not dependent upon the severity of the LVH; among the 9 cases with hearts over 900 Gm. due to LVH, 6 had a normal axis, and only 3 had LAD. In addition, he observed in his study 131 cases of LAD. When those with myocardial infarction were excluded, there were 77 remaining. He stated that only 35 of these 77 (less than half) had heart weights of 500 Gm. or more; 19 had heart weights of 400 to 500 Gm., and 23 had hearts weighing less than 400 Gm. He concluded that LAD is by no means diagnostic of LVH. It should be pointed out, however, that by most pathologic criteria, the 19 hearts weighing between 400 and 500 Gm. (and perhaps even some of those weighing less than 400 Gm. if the patients were small) would be considered in the hypertrophy range. If these were included, the incidence of LAD in Grant's series of LVH

would increase to at least 54 of the 77 cases (70 per cent). In this study and in a previous one,[7] Grant demonstrated that neither variation in body build nor variation in the anatomic position of the heart can alone be responsible for LAD. In fact, he has shown that in LVH the electrical axis may be markedly rotated to the left while the anatomic position of the left ventricle is essentially the same as in the normal heart. He emphasized that the incidence of LAD is higher among patients with anatomic LVH than it is among patients with normal hearts. He believed[32] that it is not the hypertrophy itself that is responsible for the LAD but that it is the myocardial fibrosis of the free wall of the left ventricle that may frequently accompany marked LVH. This patchy fibrosis is thought to result in an alteration in the peripheral parts of the left ventricular conduction network resulting in what is termed "parietal block." When the peripheral fibers of the anterior division of the left bundle are involved, the spread of excitation is upward from the diaphragmatic region of the left ventricle. The QRS forces then point superiorly and leftward, producing LAD in the clinical electrocardiogram. While there are other causes of abnormal LAD,[31-33] such as peri-infarction block, chronic coronary artery disease, etc., we are concerned at this time only with those that are related to LVH.

In Grant's series,[31] the voltage criteria[22] identified over 90 per cent of cases of marked LVH when the body build was normal. However, in subjects markedly overweight or underweight for their height, the criteria were totally unreliable. He cited the examples of 3 subjects with hearts weighing over 700 Gm. due to LVH with QRS complexes not more than 20 mm. in amplitude in the precordial leads; all 3 were obese. There were 7 cases with heart weights less than 450 Gm. and QRS complexes with amplitudes of more than 45 mm. in one or more precordial leads. All 7 subjects were thin and their average height was 66 inches. It should be pointed out here again, however, that some of these hearts, even though weighing less than 450 Gm., may actually have left ventricular hypertrophy. In fact, Zeek's normal heart weights for male of 168 cm. (66 in.) in length is 317 ± 40 Gm. and for females of this height is 277 ± 30 Gm.[1] Furthermore, Grant did not specify which precordial leads exhibited high voltage. This is not meant to detract from the observation that voltage criteria may be unreliable in this individuals but that the examples cited are not absolutely conclusive.

In a recent report Abdin[34] studied the relationship between the electrocardiographic changes and postmortem findings in 19 cases of aortic stenosis and in 15 cases of hypertension (without evidence of "ischemic" heart disease at necropsy). All the cases of aortic stenosis had LVH, the thickness of the left ventricle ranging from 16 to 30 mm., with an average of 21. All 15 cases of hypertension had LVH, the left ventricular thickness ranging from 18 to 25 mm., with an average of 22. Abdin found Sokolow's voltage criteria[22] for LVH to be present in all but 1 case of aortic stenosis and 1 case of hypertension. The striking feature of this study was that for comparable degrees of anatomic LVH, T-wave inversion in left ventricular leads was much more marked and frequent in aortic stenosis than in hypertension. T-wave inversion of 5 to 10 mm. occurred in 10 cases of aortic stenosis but was found in only 1 case of hypertension. He offered evidence to support the concept that the T-wave inversion in aortic stenosis is ischemic in origin and due to poor coronary flow and not to coronary artery disease.

Abdin also studied the LV/RV thickness ratio and the relation to vertical heart position and "clockwise" rotation. While a vertical heart position was common in aortic stenosis, it was less frequent in advanced cases and not necessarily related to associated RVH, since half with a vertical heart position had no anatomic RVH. In contrast, extreme "clockwise" rotation ($R<S$ in V_5) in this series was found to have anatomic RVH in each instance.

Selzer and associates[35] have quite recently

studied the effect of cardiac dilatation upon the electrocardiographic pattern of LVH. They selected 28 autopsied cases with heart weights exceeding 500 Gm., no RVH, no significant coronary artery disease, and no myocardial fibrosis or infarction. Twelve cases had pure concentric LVH and the electrocardiograph displayed LVH in 10, right bundle-branch block (RBBB) in 1, and a normal record in 1. Sixteen cases had LVH with dilatation and their electrocardiograms showed LVH in 9, bundle-branch block in 6, and no diagnostic abnormality in 1. The only trend observed was the more common occurrence of conduction defects, widening of the QRS complexes, and of LAD in the group with both hypertrophy and dilatation. Because of the wide overlapping of findings in the 2 groups, these workers concluded that the occurrence of left ventricular dilatation in addition to the pure increase in left ventricular muscle mass does not produce sufficiently characteristic electrocardiographic alterations to suggest a distinctive pattern.

Blondeau, Heller, and Lenegre[36] have quite recently reported a significant autopsy study of 136 cases of left-sided heart disease. They correlated the voltages of the QRS complexes with the weight of the left ventricle, the LV/RV weight ratio, and the degree of left ventricular thickness and dilatation. The left ventricular weight ranged from 119 to 640 Gm. and the LV/RV ratio from 1.1 to 3.8. The Lewis index, $(R_1 + S_3) - (R_3 + S_1)$, was above +17 in 30 per cent of cases and was found to be dependent upon the weight of the left ventricle. The "index" of Sokolow and Lyon was greater than 35 in 54 per cent of the cases and the sum of $RV_7 + SV_2$ was over 35 in 65 per cent. These workers observed that this appeared to be the most sensitive electrocardiographic sign of LVH. The amplitudes of the R waves in V_6 and V_7 were found to be influenced chiefly by the weight of the left ventricle while the depth of the S waves in V_1 and V_2 was dependent on the LV/RV weight ratio and also the degree of thickening and dilatation of the left ventricle.

Left Ventricular Hypertrophy in Infancy and Childhood

The electrocardiographic criteria for LVH in children are essentially the same as in adults.[22] However, because of the higher voltage normally generated in infancy and childhood and because of the thinner chest walls, the voltage requirements must exceed the maximum normal for their age.[37, 38] Nadas[39] has proposed that LVH is probably present in infants and children if R in V_5 or V_6 exceeds 35 mm., the sum of R in V_5 or V_6 plus the S in V_1 or V_2 exceeds 45 mm., the R wave in aV_L or aV_F exceeds 20 mm., the R in I plus S in III exceeds 30 or the sum of R in II and III exceeds 45 mm., or the onset of the intrinsicoid deflection in V_5 or V_6 exceeds 0.04 second. Inversion of T waves in left precordial leads with or without increase in voltage has been considered to indicate LVH in infants under 1 year of age[37] as well as in older children.[39]

To our knowledge, however, there have been no extensive autopsy-controlled studies that establish the accuracy and reliability of these criteria in infancy and childhood. We are currently engaged in such a project.

Right Ventricular Hypertrophy

The correlation of the electrocardiographic diagnosis of RVH with the pathologic findings has been studied by a number of investigators. In some series,[40, 41] although the correlation between the electrocardiogram and the clinical evidence of RVH has included a large number of cases, the number with autopsy control is small. Accordingly, such studies have not been included in detail in this presentation.

The current electrocardiographic diagnosis of RVH has been based largely upon the criteria established by Wilson,[20] Myers,[42] and Sokolow.[43] These criteria depend primarily upon changes in the right precordial leads: namely, increase in height of the R wave, decrease in depth of the S wave with an increase in the R/S ratio, delay in the onset of the intrinsicoid deflection, and ST-segment and T-wave changes. A qR pattern, as well as an rSR′ pattern has been described in right pre-

cordial leads. In the left precordial leads the R is often small with a prominent S. The total duration of the QRS is less than 0.12 second and often normal. A tall R wave in aV_R and right axis deviation (RAD) may occur.

Milnor[44] has proposed new criteria for the electrocardiographic diagnosis of RVH purported to decrease the incidence of "false positive" and "false negative" interpretations and to make possible the recognition of RVH in the presence of R′ in V_1. These criteria consist of a QRS duration less than 0.12 second and either (1) a mean frontal plane axis between +110° and ±180° or between −90° and ±180° or (2) R/S or R′/S ratio in V_1 greater than 1.0 with R or R′ greater than 0.5 mv. (5 mm.).

A summary of the studies with what we consider reasonably adequate autopsy control is presented in table 2. It can be seen, however, that even in these studies there was wide variation in the age groups included, in the etiology of RVH, in the electrocardiographic criteria employed, and whether isolated or only predominant RVH was present anatomically.

Myers and associates[42] found 7 of their 40 autopsied cases in which the electrocardiogram was not diagnostic of either RVH or a conduction defect in the right ventricle. In the cases in which the diagnosis was missed, there were 6 of cor pulmonale and 1 of mitral stenosis. These authors could find no direct correlation between cardiac weight, ventricular ratio, or thickness of the right ventricular wall and the electrocardiographic pattern.

Sokolow and Edgar[45] have correlated the electrocardiographic and pathologic findings in 38 patients with congenital heart disease. Of these, 28 cases in which the electrocardiogram showed RVH there was anatomic RVH (some of these, however, also had accompanying anatomic LVH). One case had RVH at autopsy but was not diagnosed as RVH electrocardiographically by these workers. It should be pointed out, however, that this case did display marked RAD.

Carouso and co-workers[46] found in their 58 cases abnormal alterations in the R/S ratio in V_1 and V_{5-6} suggestive of RVH in 44, and delay in the onset of the intrinsicoid deflection in V_1 in 37. These workers calculated the LV/RV weight ratio and related their findings to the disturbance in the ratio of R/S in V_1 and V_{5-6}. They found RVH in the electrocardiogram only when the LV/RV weight ratio was less than 1.2. When the R/S ratio was abnormal in both V_1 and V_{5-6}, the anatomic RVH was extreme (LV/RV of 0.78 to 0.92).

Woods[47] analyzed the electrocardiograms in 52 cases of tetralogy of Fallot and found electrocardiographic evidence of RVH in all. In 7 autopsied cases, the relative thickness of the ventricle was measured and in all there was evidence of marked RVH. However, there was no correlation between the relative thickness of the 2 ventricles and the degree of RVH in the electrocardiogram as measured by either the height of the R wave or the R/S ratio in V_1. A similar conclusion was reached by Donzelot and associates in a study of 10 cases of tetralogy of Fallot.[48]

On the basis of their study, Camerini and co-workers[49] concluded that in an adult the pattern of R>S in V_{4R} was almost invariably diagnostic and was encountered most frequently in subjects with considerable rather than slight RVH. Milnor[44] correctly diagnosed 24 of his 32 autopsied cases. Six of these would have been missed by the criteria of Myers[42] or Sokolow.[43]

Walker, Helm, and Scott[50] in their analysis of 22 cases of autopsy-proved, isolated RVH found that age, heart weight, or the LV/RV thickness ratio did not appear to influence the frequency of positive findings. Electrocardiographic evidence of RVH, however, occurred more frequently as the thickness of the right ventricle increased. In this study only 1 case with an R wave in aV_R of 5 mm., or greater, was encountered and no electrocardiogram showed an R in V_1 of 7 mm. or greater. Only 1 case had a frontal plane QRS axis greater than +110° while, of considerable interest 4 cases had LAD of −30°.

In a related study, Walker, Scott, and Helm[51] determined the reliability of the el c-

Table 2

Right Ventricular Hypertrophy

Author Year	Age Range	Pathologic criteria: Heart wt. in Gm. (range)	Pathologic criteria: Increased RV thickness or decreased LV/RV ratio	Pathologic criteria: Prep. or isolated RVH	Etiology: MS	Etiology: CP	Etiology: Cong.	Etiology: Other	ECG criteria employed	rSR′ pattern in right precordial leads	No. of autopsied cases	Positive ECG diagnosis	Accuracy of ECG diagnosis of RVH (per cent)
Myers et al.[42] 1948	15-82 yrs.	284-700	↓LV/RV Ratio	Prep.	13	24	3	—	Myers[42]	Included	40	30 (9IRBBB)+ 3CRBBB	75
Sokolow and Edgar[45] 1950	3 mos.-27 yrs.	—	↑Thickness	Prep.	—	—	29	—	Sokolow[43]	Excluded	29	28*	97
Carouso et al.[46] 1951	—	230-630	↑Thickness ↓LV/RV Ratio	Prep.	22	31	2	3	Lewis[2] Wilson[20] Myers[42] Sokolow[43]	Included	58	44 (24IRBBB)	76
Levine and Phillips[20] 1951	—	—	↑Thickness	—	—	—	—	—	Wilson[20] Myers[42]	—	10	8	80
Woods[47] 1952	—	90-270	↑Thickness	Isolated	—	—	7	—	Myers[42]	None encountered	7	7	100
Camerini et al.[49] 1956	Adults	—	↑Thickness	Isolated	—	—	—	—	Myers[42] +V4R	Included	31	13 (2IRBBB)+ 1CRBBB 1LBBB	42
Walker et al.[50] 1955	15-79 yrs.	315-675	↑Thickness	Isolated	5	—	1	16	Myers[42] Sokolow[43]	Included	22	5 (1IRBBB)	23
Milnor[44] 1957	>1 yr.	>25% of normal	↑Thickness	Isolated	14	12	6	—	Milnor[44]	Included	32	24	75
Bialostozky et al.[52] 1957	4 mos.-65 yrs.	45-600	↑Thickness	Prep.	4	4	8	—	Braunwald[40]	—	16	14	88
Phillips[53] 1958	46-76 yrs.	375-750	↑Thickness	Prep.	—	18	—	—	Sokolow[43] Milnor[44] Scott[54] Braunwald[40]	Included	18	7-13	38-72
Hollman[54] 1958	1 mo.-15 yrs.	Not given	Not given	Isolated	—	—	29	—	Hollman[54]	Included	29	25	86
Evans and Short[56] 1958	15-52 yrs.	280-700	↑Thickness	Both	—	—	10	—	Evans and Short[56]	Included	10	10‡	100‡

RV: right ventricular; LV/RV: left ventricular/right ventricular ratio; Prep.: preponderant; MS: mitral stenosis; CP: cor pulmonale; Cong.: congenital; IRBBB: incomplete right bundle-branch block (rSR′); CRBBB: complete right bundle-branch block; LBBB: left bundle-branch block.

*See text.

‡See text (2 cases with CVH).

trocardiographic pattern of RVH. Tracings showing RBBB were excluded. Twelve adult cases that fulfilled these criteria and had autopsy examination including a determination of heart weight and ventricular wall thickness were analyzed. Eight of the 12 demonstrated RVH anatomically. A surprising finding in the study was that 4 cases had anatomic LVH.

Bialostozky and associates[52] found the electrocardiographic criteria for RVH as proposed by Braunwald and associates[40] to be positive in 14 of 16 autopsy-proved cases of isolated RVH.

Phillips[53] has recently made some interesting observations on the electrocardiographic changes in cor pulmonale secondary to pulmonary emphysema. Employing different sets of electrocardiographic criteria used by previous authors,[40, 43, 44, 54, 55] he analyzed the electrocardiograms in 18 cases in which autopsy disclosed anatomic RVH. He emphasized that the electrocardiographic criteria for the diagnosis of RVH depend upon 2 basic changes in the electrical forces: their orientation toward the right and their orientation anteriorly. He postulated that a pattern of evolution of the electrocardiogram of cor pulmonale occurs in 3 stages. In the first stage, the major electromotive forces are directed leftward and posteriorly (normal electrocardiogram). In the second stage there is rightward but still posterior direction of the major electromotive force (RAD, prominent S waves in left precordial leads). In the third stage there is anterior as well as rightward direction of the mean spatial vector (tall R waves over the right chest as well as RAD). Patients in this last category of his series had the heaviest hearts with the thickest right ventricular walls. He concluded that those electrocardiographic criteria for RVH that depended primarily on anteriorly directed forces tended to detect only the more advanced forms of RVH, whereas those criteria that were based on the rightward (although still posterior) direction of the mean spatial vector tended to detect lesser degrees of RVH. Some 30 per cent of his cases, however, were missed by all criteria.

Evans and Short[56] have reported the clinical and pathologic features in 11 patients with congenital heart disease and pulmonary hypertension. Only 10 of these, however, had electrocardiograms for comparison with the pathologic findings. Eight cases exhibited RVH in the electrocardiogram and 2 CVH. At autopsy the 8 cases had either isolated or preponderant RVH and the 2 had CVH although the RVH was proportionately greater.

Other studies with anatomic and electrocardiographic correlations have been carried out but sufficient specific details have not been given in these reports to be included in table 2. A brief consideration of some of these studies will now be made.

Thomas[57] studied at autopsy 50 hearts from coalminers with pneumoconiosis, employing the method of Herrmann and Wilson[3] for dissecting and weighing the right and left ventricles. The total heart weights ranged from 180 to 800 Gm. He considered an LV/RV ratio below 1.40 and above 2.20 as abnormal. While there were many small hearts in the series, right ventricular preponderance by actual weight was present even in the smallest hearts. It was noted that hypertrophy was first evident in the thickening of the muscle around the base of the outflow tract, particularly the crista supraventricularis. Only 18 of these cases had electrocardiograms available and a detailed correlation was not given. Four cases with electrocardiographic patterns of RVH had LV/RV ratios below 1.00 while 2 cases with LV/RV ratios of 1.00 and 1.02 did not display RVH in the electrocardiogram. One of these cases had a small heart, the right and left ventricles each weighing 91 Gm. Thomas suggested that the LV/RV ratio must be below 1.00 before the electrocardiographic pattern of RVH can be expected. He concluded that while there is a great degree of RVH usually found in the advanced cases of pneumoconiosis, the electrocardiographic patterns are a poor index of early RVH.

Fraser and Turner[58] have conducted an extensive survey of the electrocardiogram in mitral valve disease including 200 cases in their operation series and 38 cases in their post

mortem series. We are here concerned only with the latter group. They encountered 13 patients with anatomic RVH but no evidence of this electrocardiographically. All 14 cases with R/S>1 in right ventricular leads had anatomic RVH. All 11 cases with R>7 mm. in V_1 irrespective of the R/S ratio had marked anatomic RVH. Four of their cases showed a Q in V_1, and the right ventricular thickness ranged from 9 to 12 mm. in these cases. Of especial interest in this study was the occurrence of 11 cases of incomplete RBBB and at autopsy all had definite RVH. In this study there were 18 patients in which the thickness of the right ventricle was 8 to 12 mm. and in this group the height of the R wave in leads over the right ventricle varied between 1 and 15 mm. and the R/S ratio from 0.1 to 11.0.

These workers found a striking lack of correlation between the electrocardiographic and anatomic evidence of RVH. They noted particularly the poor correlation between the better developed electrocardiographic signs of RVH and the more pronounced degrees of anatomic RVH. They concluded that electrocardiographic signs in mitral stenosis do not occur until hypertrophy is marked and that in mitral stenosis anatomic hypertrophy is frequently less severe than in congenital heart disease.

Fraser and Turner also discussed some of the difficulties encountered in accurate correlation between electrocardiographic and anatomic findings. They pointed out that the electrocardiographic signs of RVH are not in direct proportion to the thickness of the ventricular wall beneath the exploring electrode. Of considerable interest were the findings of Fraser and Turner of anatomic and electrocardiographic RVH in occasional cases of predominant mitral insufficiency. Studies by Bentivoglio and associates[59, 60] have also confirmed the phenomena of RVH in some cases of mitral insufficiency. The RVH has been attributed to disproportionate rise in the left atrial pressure with ensuing pulmonary hypertension and pulmonary vascular changes.[59]

It thus appears that the accuracy of the electrocardiographic diagnosis of RVH has varied from 97 to 100 per cent in the cases of congenital heart disease[45, 47, 56] to a low of 23 per cent in our series of isolated RVH.[50] Most workers agree that the electrocardiographic criteria for RVH are more frequently positive in RVH due to congenital heart disease than to acquired heart disease. On the other hand, it has been pointed out that the criteria of Sokolow and Lyon[43] are too broad and would include as RVH many instances of normal hearts, especially in children.[40, 44] In fact, modified criteria should be used for the diagnosis of RVH in infancy and early childhood.

Right Ventricular Hypertrophy in Infancy and Childhood

The electrocardiographic diagnosis of RVH in infancy is difficult because of the normal right ventricular preponderance found in this age group. While it has been generally accepted that the right ventricle in the newborn is of approximately the same or of even greater thickness than the left ventricle, there is considerable lack of agreement as to the exact age when the adult proportions between the right and left ventricles are reached.

Barry and Patten[61] stated that after birth the left ventricle begins to assume its characteristic preponderance and by the fourth year of life adult proportions are attained. Lepeschkin[62] commented that the right ventricular wall has become normal at the end of the first year, although his graph shows that the major change has occurred by the sixth month. Keen[63] found the adult proportions between the left and right ventricle to be present by the third to fifth month although there was a progressive increase in the left-to-right ratio up to 12 months. According to Hollman[64] the ratio of the right to the left ventricular thickness is 6 to 7 at birth, after 3 months the left ventricle starts to become dominant, and by the age of 6 years the normal adult left ventricular dominance is largely established. On the other hand Edwards[65] stated that by the end of the third postnatal month the adult disproportion between the thickness of the 2 ventricles is established.

Sodi-Pallares and associates[66] have pre-

sented recent evidence that in infants there is in fact no right ventricular predominance in the parietal thickness, but that the right ventricular free wall is thinner than the left and there is no great difference between the ventricles as in adults. As age progresses, the increase in thickness is more important in the left ventricular wall than in the right. The electrocardiographic pattern of right ventricular preponderance normally found in the newborn and infant undergoes a gradual transition with increasing age toward the adult type of electrocardiogram, which is characterized by left ventricular dominance.

There is a more or less gradual progression of the mean electrical axis from approximately +120° in the first month of life to between +60° and +90° at the age of 6 months, where it remains throughout the remainder of childhood.[37] The R waves are small in leads I and II during the first month and increase to approximately adult amplitude between the ages of 3 and 6 months.[37] While the older reports[2, 67] concluded on the basis of the standard-lead changes that the adult proportions between the right and left ventricles were reached by about the third to sixth month of life, Ziegler[37] has emphasized that regardless of the extremity-lead pattern no definite conclusion may be made concerning the relative size of the 2 ventricles.

The precordial electrocardiogram in normal infants from birth to 3 years has been shown by Ziegler[68] to include (1) evidence of a normal degree of relative right ventricular preponderance, consisting of large amplitude R waves with late onset of the intrinsicoid deflection in right precordial leads, (2) presence of upright T waves in leads from the right side and inverted T waves in left chest leads during the first 24 hours of life followed by a gradual progression to inverted T waves in right precordial leads and upright T waves in left precordial leads during the subsequent 2 to 4 days. The average amplitude of R in V_1 exceeds that of lead V_6 from birth to approximately 6 months; they are nearly equal from 6 months to 1 year; beyond the age of 1 year the amplitude of R in V_6 exceeds that of lead V_1.[37] The R wave is dominant in V_1 (R/S ratio greater than 1) in the majority of infants during the first 1 to 3 years of life.[37, 39, 62, 66, 69] After the age of 3 the majority of children will show an R/S ratio less than 1 in V_1, although occasionally this may not occur until the age of 5 or even older. The majority of normal children will have a dominant S wave in V_1 by the age of 5.[39] Thus the right ventricular dominance of the normal infant gradually gives way to left ventricular dominance by the age of 3 years although this may be normally delayed in some cases until 5 years or even older.[37, 69]

Lepeschkin[62] has observed that the R/S ratio in precordial leads, the degree of RAD, and the relative thickness of the right ventricular wall show an almost identical course during growth. Ziegler,[37] however, has cautioned against attempting to make too close a correlation between the electrocardiogram and the anatomic measurements in infants and children.

The diagnosis of abnormal right ventricular enlargement in the newborn and the infant under the age of 3 is thus attended by certain difficulties not present in the adult. Nevertheless, electrocardiographic criteria for the diagnosis of RVH in infants have been well defined.[38, 39, 41, 70–73] The more important of these proposed criteria may be briefly summarized: (1) a single-peaked RS deflection followed by a positive T wave in right precordial leads after the first 48 hours of life; (2) a monophasic R or a qR pattern with an upright (or inverted) T wave in right precordial leads; (3) an rSR′ (with R′ greater than 10 mm.) or a notched or double-peaked R, the amplitude of which is 85 to 100 per cent of the RS and followed by an inverted T wave in right precordial leads; (4) delay in the onset of the intrinsicoid deflection of 0.03 second or more in right precordial leads; (5) a dominant late R wave in aV_R (in a vertical heart); (6) RAD of +120° or greater; and (7) so-called "barrage" type of Donzelot with pattern of RVH plus RBBB extending across the entire precordium. Since an upright T wave may occur normally in V_1 at

age 12, there is a group between 1 and 12 years of age in whom RVH may be suspected from the presence of an upright T in V_1.[38]

Goodwin[70] studied 36 children from 3 to 14 years of age with congenital heart disease and presumed RVH. He suggested that the important signs of RVH are an R/S ratio greater than 1 with a ventricular activation time greater than 0.03 second in V_1 and a Q/R ratio less than 1 in aV_R. Three of these cases came to autopsy and RVH was found in each.

Hollman,[64] however, pointed out that the R/S ratio in V_1 may be over 1.0 in normal children up to the age of 10 years. In infants under 3 months the R/S ratio is normally quite high.[64] The R/S ratio in V_5 in this age group normally, however, is always 0.6 or greater while in RVH it is 0.5 or less,[64] this being of particular value in the diagnosis of RVH in the very young. Hollman[64] has proposed criteria for the diagnosis of RVH from 1 month to 15 years of age, which include (1) the presence of a Q wave in V_1; (2) onset of intrinsicoid deflection in V_1 of 0.04 second or greater in the absence of RBBB; (3) R/S or R/Q in aV_R greater than 1.0; (4) P wave of 3 mm. or more in lead II or 2.5 mm. or more in any other lead; (5) electrical axis of over +120°; and (6) R/S in V_1 and V_5 which equal or exceed the following ratios:

	1-3 months	4-11 months	1-2 years	3-5 years	6-15 years
R/S V_1	7.0	4.5	2.5	2.0	1.5
R/S V_5	0.5	0.7	0.8	0.9	0.9

Hollman evaluated the accuracy of these criteria in 29 autopsy-proved cases of isolated RVH in children ranging from 1 month to 15 years. He found 2 or more criteria present in 25 cases (85 per cent). In the remaining 4 cases 1 criterion was satisfied in each and he classified them as having probable RVH.

The rSR′ Pattern in Right Precordial Leads

The rSR′ pattern in right precordial leads with a QRS duration less than 0.12 second may occur in normal subjects,[74, 75] in RVH,[42, 76] in right ventricular dilatation,[42, 76] in so-called right ventricular diastolic overload,[77] in incomplete right bundle-branch block (IRBBB),[20, 78, 79] in IRBBB and RVH,[44, 78] in coronary artery disease,[44] and in anterolateral peri-infarction block.[31, 33]

The secondary r wave encountered in some normal subjects has been attributed to normal variation in the order of ventricular activation,[75] activation of the pulmonary conus,[74] or crista supraventricularis.[80] In fact, it has been suggested that in the majority of healthy young adults final activation occurs in the base of the septum or right ventricle.[81] The electrocardiographic pattern characterized by late secondary R waves in aV_R and in right chest leads is indistinguishable from or identical with certain types of IRBBB as described by Barker and Valencia.[78, 81] Some workers believe that the rSR′ pattern may represent an intermediate stage in the development of electrocardiographic signs of RVH and that it is not necessarily associated with a conduction defect.[82, 83] Evidence has been presented to suggest the concept that the rSR′ observed in atrial septal defect[84] as well as in certain other congenital and acquired lesions is due to hypertrophy of the outflow tract or crista supraventricularis rather than to IRBBB.[80, 85-87]

Camerini, Goodwin, and Zoob[49] encountered the rSr′ in V_{4R} in 5 cases and rSR′ in 2 cases of anatomically proved RVH. They considered the rSr′ pattern not to be diagnostic while the rSR′ pattern was suggestive of RVH. Myers and co-workers[42] encountered 9 cases that satisfied their criteria for IRBBB among 40 cases of autopsy-proved RVH. The findings of Fraser and Turner[58] have already been cited. Barker and Valencia[78] have proposed that in the presence of the pattern they refer to as IRBBB (rSR′) if R′ is 10 mm. or greater, RVH coexists. In complete right bundle-branch block (CRBBB) if R′ is 15 mm. or greater, RVH is also present.[88] Carouso and associates[46] in their study of 58 cases of isolated RVH proved at autopsy, encountered 24 with IRBBB (rSR′). Of these, only 3 had an R′ greater than 10 mm. Milnor and Bertrand[83] found in their study of atrial septal defect that in 2 of 5 cases with RSR′

there was isolated RVH while in the other 3 there was CVH. They further observed that conduction delay must play a part in the pathogenesis of the RSR′ in V_1 in some instances but in the absence of direct evidence, it was not justifiable to assign the site of conduction delay to the "bundle branches."

In a controlled study (but one without autopsy correlation) Dodge and Grant[79] analyzed the electrocardiogram before and after the development of RBBB (QRS duration of 0.12 second or longer in this study). In none of the control tracings was there evidence of RVH. After the occurrence of RBBB, however, these workers found that R′ in V_1 ranged from 4 to 12 mm. in 90 per cent of their 80 cases and was 20 and 23 mm. in 2 cases. They thus demonstrated the range of deformity that RBBB may produce in the absence of electrical evidence of RVH. They concluded that the magnitude of the deflection of the last 0.04 second must exceed these values in RBBB before the diagnosis of RVH plus RBBB can be made.

Fowler[89] has observed the occurrence of tall secondary R waves in right precordial leads in 5 of 7 cases that developed induced complete RBBB as a complication of right heart catheterization. The R′ in V_1 ranged from 12 to 20 mm. in height and was 15 mm. or more in 3 instances. In all of these cases, the RBBB disappeared within 24 hours and in none was there any electrocardiographic evidence of RVH either before or after the RBBB.

Vector studies of the rSR′ pattern have shown what Grishman and associates[90–93] believed to be a differential pattern in the horizontal plane: namely, clockwise rotation with a slowly inscribed terminal phase indicating RVH with RBBB. More recent studies,[44, 94] however, suggest that there are no loop rotations that may be considered as exclusively representative of RBBB.

Booth, Chou, and Scott[95] evaluated the accuracy of the electrocardiographic diagnosis of ventricular hypertrophy in the presence of RBBB in a series of 49 cases, correlating the electrocardiogram with the postmortem findings. The electrocardiographic diagnosis of RBBB was made by conventional criteria including a secondary R wave in right precordial leads exceeding the initial R wave in height. The block was deemed complete if the QRS duration was 0.12 second or greater and incomplete if the QRS duration measured 0.08 to 0.11 second, inclusive. The tracings were analyzed as to the presence of associated RVH by the criteria of Barker and Valencia.[78] The electrocardiographic diagnosis of LVH was made by means of current criteria.[27] In this series of 49 cases, unselected as to anatomic diagnosis, 4 (8 per cent) had isolated RVH, 15 (30.5 per cent) had isolated LVH, 22 (45 per cent) had CVH, 6 (12.5 per cent) had normal hearts, and 2 had increased heart weight but normal ventricular wall measurements.

The correlation of the electrocardiograms with the autopsy findings is shown in table 3. Twenty-six of our cases of IRBBB were analyzed according to Milnor's criteria[44] for the diagnosis of associated RVH. Fifteen of the 26 met Milnor's criteria for RVH on the electrocardiogram. The diagnosis was correct in 9 (60 per cent) and erroneous in 6 (40 per cent). In addition 7 cases of anatomic CVH were missed as was 1 case of isolated RVH. A total of 11 cases met the criteria of Barker and Valencia[78] for associated RVH. The right ventricle was enlarged in 7 of these cases (63.5 per cent) although in 4 of these LVH was also present. Unexpected findings in this study were the high incidence (37 cases) of anatomic LVH and the consistency with which the diagnosis was missed in the electrocardiogram. The electrocardiographic diagnosis of LVH was obscured in all by the RBBB. One case that fulfilled the electrocardiographic criteria for LVH revealed isolated RVH at autopsy. The results of this study are in agreement with Myers,[42, 76] who indicated that RBBB is associated with enlargement of the left ventricle, either alone or in combination with RVH, in too many cases to render it a significant sign of an isolated right ventricular lesion.

An attempt was made in this study[95] to correlate the electrocardiographic diagnosi

Table 3

A Correlation of the Electrocardiographic Diagnosis with the Postmortem Findings in Forty-nine Cases of Right Bundle-Branch Block

Electrocardiographic diagnosis			Anatomic findings				
			RVH	LVH	CVH	NVH	IWNM
IRBBB (28 cases)	RVH	8	2	1	3	1	1
plus	LVH	1	1	0	0	0	0
	CVH	1	0	1	0	0	0
	NVH	18	0	5	11	1	1
CRBBB (21 cases)	RVH	3	1	1	1	0	0
plus	LVH	0	0	0	0	0	0
	CVH	0	0	0	0	0	0
	NVH	18	0	7	7	4	0
Total		49	4	15	22	6	2

IRBBB, incomplete right bundle-branch block; CRBBB, complete right bundle-branch block; RVH, right ventricular hypertrophy; LVH, left ventricular hypertrophy; CVH, combined ventricular hypertrophy; NVH, no ventricular hypertrophy; IWNM, increased heart weight with normal ventricular measurements.

of right, left, or no ventricular preponderance with the LV/RV thickness ratio. Such an analysis failed to reveal the expected relationship that increasing mass of one ventricle would produce a more frequent electrocardiographic diagnosis of preponderance of that chamber. It was further observed that attempts to relate the height of the R′ wave over the right precordium to the ratio LV/RV thickness revealed no correlation between the voltage produced over the right precordium and the relative preponderance of the left or right ventricle.

Combined Ventricular Hypertrophy

The electrocardiographic diagnosis of CVH is ordinarily based upon the conventional criteria for isolated LVH and RVH in the precordial and unipolar extremity leads.[20, 22, 42, 43] In addition, RAD greater than +90°, marked displacement of the transition zone to the left, and the presence of a vertical or semivertical heart in the presence of electrocardiographic evidence of LVH have been considered suggestive of associated RVH. Nevertheless, as can be seen in table 4, electrocardiographic patterns considered diagnostic of CVH are encountered rather infrequently in cases with anatomic CVH. Soulié and associates[96] established electrocardiographic criteria of CVH on the basis of 57 cases, 27 of which were autopsied. The pattern that they considered pathognomonic was RAD greater than +90°, marked "clockwise" rotation, and signs of RVH and LVH in the precordial leads. Only 4 of their cases satisfied these criteria. Levine and Phillips[26] concluded that CVH is rarely detected in the electrocardiogram.

Pagnoni and Goodwin[97] found that direct evidence of RVH (increased ventricular activation time and R>S in V_1) was masked by LVH. These workers considered an R>Q in aV_R, S>R in V_5 with T-wave inversion in V_1, together with signs of LVH, diagnostic of CVH, while the association of a vertical heart position with signs of LVH were highly suggestive of CVH. Sokolow and Edgar[45] observed that when CVH was present anatomically, the electrocardiogram usually reflected the change in the ventricle with the major hypertrophy. They further found that when ventricular hypertrophy was minimal, a normal or borderline electrocardiogram was occasionally found. Lipsett and Zinn[98] in a study of 73 patients with necropsy evidence of CVH found only 10 cases with electrocardiographic evidence of CVH and concluded that the diagnosis is difficult. They found that RVH resulting from cor pulmonale could be diagnosed more frequently than RVH resulting

Table 4

Combined Ventricular Hypertrophy

Author Year	Number of cases with anatomic CVH	ECG diagnosis			Accuracy of ECG diagnosis of CVH %
		CVH	LVH	RVH	
Soulie et al.[96] 1949	27	4			15
Levine and Phillips[20] 1951	26	2	12	1	8
Pagnoni and Goodwin[97] 1952	51	13	13	10	26
Lipsett and Zinn[98] 1953	73	10	21	26	14
Levine and Whipple[99] 1955	8	3	3	1	38
Fraser and Turner[58] 1955	22	3	2	11	14

CVH, combined ventricular hypertrophy; LVH, left ventricular hypertrophy; RVH, right ventricular hypertrophy.

from rheumatic or hypertensive heart disease when LVH was also present. They related this to the more significant RVH present in their cases with cor pulmonale. Whipple and Levine[99] studied the electrocardiogram (and vectorcardiogram) in 9 cases of CVH proved at autopsy. It is of interest that they observed while LVH in a vertical heart occurred in 2 instances, there were no cases in which the precordial transition zone shifted significantly or prominent R waves in aV_R occurred. Fraser and Turner[58] encountered 22 cases of anatomic hypertrophy of both ventricles in their study of mitral valve disease. These workers found that considerable anatomic biventricular hypertrophy may exist in association with electrocardiograms showing RVH alone (11 cases) or without evidence of either RVH or LVH (6 cases). In 2 cases with electrocardiographic evidence of LVH alone the anatomic LVH was proportionately greater than the RVH, and the former seemed to mask the electrocardiographic signs of RVH. They suggested that from the electrical point of view RVH and LVH may "balance" each other and no ventricular hypertrophy be evident in the electrocardiogram.* They found, however, no obvious relationship between the degree of hypertrophy in the ventricles and the presence or degree of electrocardiographic signs of biventricular hypertrophy. They concluded that electrocardiographic signs of CVH are uncommon in patients with rheumatic heart disease, even though such hypertrophy may be marked at autopsy.

Ventricular Hypertrophy in the Presence of Left Bundle-Branch Block

The electrocardiographic diagnosis of LVH in the presence of complete left bundle-branch block (LBBB) has been considered difficult, if not impossible,[88] although some workers[8] believe that this diagnosis can be made. We have recently studied this problem in our laboratory and compared the accuracy of the electrocardiographic diagnosis with the pathologic findings.[100] All cases with the diagnosis of LBBB in which an autopsy had been performed were collected. All cases with pathologic evidence of myocardial infarction were excluded. The conventional electrocardiographic criteria of high voltage for LVH were employed and the pathologic criteria for ventricular hypertrophy have already been defined.

Twenty-eight cases of LBBB were studied. At autopsy all cases had cardiac hypertrophy. Only 10 of the 28 cases showed electrocardiographic evidence of LVH. At autopsy 3 of these had pure LVH and 7 had CVH. Eight cases of pure LVH at autopsy showed no electrocardiographic evidence of LVH. It would appear on the basis of this study that the precise electrocardiographic diagnosis of LVH in the presence of LBBB is difficult and unreliable. Massive RVH and LBBB rarely occur together, according to Wilson.[20] We are planning to investigate this uncommon combination of findings.

Ventricular Hypertrophy and Myocardial Infarction

Myers[101, 102] has emphasized that ventricular hypertrophy occasionally presents electro-

*Ziegler,[72] however, believed that RVH and LVH do not "balance" out to give a normal electrocardiogram.

cardiographic patterns that may mimic those of myocardial infarction. He presented 10 cases of LVH[101] in which no evidence of infarction was demonstrated at autopsy, yet one or more of the following electrocardiographic features were encountered which suggested infarction: (1) deep Q waves, marked ST-segment depression, or sharp inversion of the T waves in left ventricular leads; (2) abnormal Q waves, bizarre ST-segment shifts, or cove plane inversion of the T waves in the transitional zone; (3) QS pattern or abnormal S-T elevation in right precordial leads.

In a related study Myers presented 15 cases proved at autopsy of RVH or right ventricular dilatation without myocardial infarction.[102] The electrocardiograms in these cases presented one or more of the following features that resembled a pattern of myocardial infarction: (1) abnormal qR or QS patterns or sharp T-wave inversion in right precordial leads; (2) reduction in amplitude of the R waves or replacement by a QS deflection or change from an upright to an inverted T wave as the transition zone was reached; (3) persistence of normal Q waves in left ventricular leads accompanied by marked reduction in the R wave and exaggeration of the S wave.

Goodwin[103] has studied the relationship between ventricular hypertrophy and myocardial infarction. His material was highly selected in that he included only those cases that had evidence at autopsy of myocardial infarction, RVH or CVH, and whose electrocardiograms displayed predominantly negative deflections in V_5 (rS, Qr, QS, or qrS). His 85 cases were grouped as isolated hypertrophy, isolated infarction, or both hypertrophy and infarction. In analyzing his tracings for distinguishing features, he found that the classic pattern of wide deep Q waves with S-T elevation and T-wave inversion in V_5 was encountered in infarction with or without hypertrophy but in only 1 case of isolated RVH. On the other hand the rS pattern in V_5 occurred in isolated infarction, isolated hypertrophy, or in both hypertrophy and infarction. Features favoring infarction included diagnostic evidence in other leads, a negative T wave in V_5, a positive T wave in V_1, or S-T elevation greater than 2 mm. By contrast, a vertical heart position and "right atrial" P waves (pointed P waves of 2.5 mm. or more) suggested isolated or dominant RVH. Right atrial P waves were not encountered in any case of infarction, and a vertical heart was only seldom encountered in infarction (12 per cent) while rather commonly encountered in the cases of hypertrophy without infarction (66 per cent).

Goodwin[103] pointed out that while the commonest cause of a deep S wave in V_5 is isolated or dominant RVH, it may also occur in anterior infarction with or without RVH. Thus, any electrocardiogram showing the rS pattern in V_5 should be interpreted with caution and the possibility of a concealed infarct considered. On the basis of this study he also concluded that the classic patterns of anterior infarction (QS with S-T elevation and T-wave inversion) were less common when RVH was present than when infarction occurred in the absence of RVH. The most important factors concerned with the production of the rS pattern in anterior infarction were thought to be associated RVH and changes in the healing of the infarct.

Burch and associates[104] have recently reported a correlative study of the electrocardiogram (and spatial vectorcardiogram) with the findings at autopsy in 59 patients with myocardial infarction. Of 33 cases with posterior myocardial infarction, 18 had proved ventricular hypertrophy. The 1 case with anatomic RVH showed electrocardiographic RVH; 6 cases with anatomic LVH showed electrocardiographic LVH in 4; 11 cases of anatomic CVH showed 1 with electrocardiographic CVH, 7 with electrocardiographic LVH, and 1 with RBBB. There were 2 cases in this group of posterior infarction with the electrocardiographic criteria of RVH without anatomic evidence of RVH.

Of 26 cases with anterior myocardial infarction 21 had anatomic ventricular hypertrophy. One case with anatomic RVH displayed electrocardiographic RVH; 7 cases

with anatomic LVH displayed electrocardiographic LVH in 3; 13 cases of anatomic CVH showed 2 with electrocardiographic CVH, and 5 with electrocardiographic LVH. There was 1 instance in this group with anterior infarction of a false diagnosis of LVH. The anterior infarct was missed electrocardiographically in 1 of the hearts with ventricular hypertrophy.

These authors concluded that the diagnosis of ventricular hypertrophy by the electrocardiogram was unreliable. They attributed this in part to the high incidence of combined hypertrophy with the electric effects of one chamber tending to neutralize the other. They also called attention to the observations of den Boer,[105] that the difficulty in distinguishing LVH from anterior myocardial infarction may be due to the fact that in both conditions the resultant of the electric dipoles points backward and to the left.

Electrophysiologic and Anatomic Considerations

General

The exact electrophysiologic mechanisms that are responsible for the electrocardiographic phenomena that occur in ventricular hypertrophy are not entirely clear.[7, 8, 20] Hypertrophy results in an increase in the ventricular muscle mass and in the length and thickness of the wall of the involved chamber.[7, 20] There is also an increase in the total epicardial surface area and an increase in size of the individual muscle fibers.[20] Perhaps there may be a diminution in the density of the juncture between the Purkinje fibers and the subendocardial muscle, as well as an increase in the path traversed by the excitation wave.[20] It has also been suggested that the myocardial fibrosis which may occur in ventricular hypertrophy may perhaps produce an alteration in the more peripheral parts of the conduction system.[31]

An increase in the number of activation dipoles with oblique spread of the epicardial QRS vector,[7, 106] increased voltage generated by the individual, hypertrophied muscle fibers,[20] closeness of the hypertrophied and frequently dilated ventricular chamber to the chest wall,[8] and increased surface area with increase in magnitude of vectors generated from this region[7] have all been proposed as explanations for the increase in voltage that accompanies ventricular hypertrophy.

The increase in voltage, the increase in duration of the QRS complex, and the delay in the onset of the intrinsicoid deflection are ordinarily attributed to delay in the transmyocardial excitation wave because of increase in muscle mass and thickness of the free ventricular wall.[7, 8, 107] So-called parietal wall conduction defects of a minor degree may play a role in some cases.[31] The increased thickness and mass of the hypertrophied ventricle may permit it to generate forces that abnormally overbalance as well as outlast the forces produced by the opposite ventricle.[20]

The S-T depression and T-wave inversion that often accompany increased voltage of the QRS complex in ventricular hypertrophy have ordinarily been attributed to the increased thickness of the muscular walls[8] with altered direction of recovery. These S-T segment and T-wave changes have been considered by some to be secondary to the large QRS complexes, while these alterations have been considered by others actually to represent primary changes due to myocardial disease.[8, 20]

While anatomic rotation of the heart has been invoked for various electrocardiographic changes encountered in ventricular hypertrophy,[8, 25, 62, 88] Grant has shown in a careful anatomic-electrocardiographic study that there is rarely more than a 20° variation in the anatomic long axis of the left ventricle in either the normal subject or the subject with marked RVH or LVH, regardless of body build.[7, 18]

Left Ventricular Hypertrophy

The genesis of the electrocardiographic patterns that occur in LVH is still obscure. As already indicated, various explanations have been offered for the electrocardiographic changes encountered in ventricular hypertrophy but the precise electrophysiologic mechanisms must await further investigation.

lowever, it may be well to review briefly ome of the more cogent, currently accepted iews as they apply to LVH.

First, however, let us consider the anatomic lterations that occur in LVH. It is well estabished from pathologic studies[1-7, 108] that there s an absolute increase in muscle bulk or veight of the left ventricle, there is an inrease in thickness of the free wall as well as f the interventricular septum, and an elongaion of the left ventricular chambers. Furhermore, it has been demonstrated[108] that the liaphragmatic and anterior portions of the eft ventricle do not change appreciably in ontour with the development of LVH, presumably because they are limited by the diaphragm and the outflow tract of the right ventricle respectively. However, the posterior and superior surfaces of the left ventricular wall are unrestrained and show the most marked alteration, becoming bowed and elongated.[7, 108] In LVH the internal architecture of the left ventricle is not significantly altered[33] aside from hypertrophy of the papillary muscles and the trabeculae carneae. Histologically there is an increase in size of the individual muscle fibers although a moderate degree of hypertrophy is required before it is apparent microscopically.[109] In myocardial hypertrophy there is apparent failure of the blood supply to parallel the growth of the muscle fibers. The ratio of 1 capillary to 1 muscle fiber in the adult persists, no matter how large the heart becomes, producing what probably is relative coronary insufficiency in the enlarged heart.[12, 110, 111] Some cases of LVH show a considerable increase in the interstitial connective tissue.[33, 88]

When hypertrophy produces a symmetrical hickening of the wall of the left ventricle, it s ordinarily referred to as "concentric hypertrophy."[12, 108] When hypertrophy becomes arked or is complicated by dilatation, the pical portion of the left ventricular chamber ecomes thinner than the wall at the base. his condition is referred to as "eccentric ypertrophy."[12, 108] When dilatation of the ft ventricle occurs it has also been observed involve more markedly the portions of the chamber that lie in front of the anterior leaflet of the mitral valve; thus the outflow tract and superior wall of the left ventricle may be more markedly stretched and bowed than the inflow tract and inferior wall.[108]

The conventional electrocardiographic criteria for LVH include increase in voltage (tall R waves in left precordial leads, deep S waves in right precordial leads, tall R waves in aV_L in horizontal hearts, tall R waves in aV_F in vertical hearts), delay in ventricular activation time in left precordial leads, slight increase in width of the QRS interval, and ST-segment and T-wave displacement opposite in direction to the major QRS deflection. While LAD may occur in LVH with tall R waves in lead I and deep S waves in lead III, normal axis deviation is common, and even RAD may be encountered.

Many explanations have been advanced for the genesis of the electrocardiographic alterations that occur in LVH. These have been well presented in several publications.[8, 33, 62, 88] It will suffice here to summarize the more likely explanations.

The prolongation of the QRS as well as the delay in ventricular activation time is ordinarily attributed to the increased thickness of the left ventricular wall with the consequent increase in time for the activation process to spread through the myocardial wall. Wilson and Herrmann[107] demonstrated many years ago that there was a relationship between increasing ventricular weight and thickness of the left ventricular wall and increasing duration of the QRS interval. These workers, however, believed that an increase in the QRS interval beyond 0.10 second should not in general be ascribed to increased size of the heart or increased thickness of the left ventricle alone but to an intraventricular conduction defect. This has also been affirmed by Bayley.[112]

The propagation of excitation over the Purkinje network was estimated by Lewis and associates[113-115] to be 4,000 mm. per second while in the ventricular walls only 400 mm. per second. More recent studies,[8, 116, 117] however, give the rate of Purkinje propagation at

about 1,000 mm. per second and ventricular wall conduction at about 300 mm. per second. It would appear that marked increase in thickness of the ventricular musculature would result in slower transmyocardial spread of the activation wave. The exact depth of penetration of the Purkinje network into the myocardial wall is unsettled but it has been suggested that these fibers penetrate deeply into the muscular wall of the left ventricle,[8, 118] although this has never been demonstrated anatomically in the human heart.[119] In fact, Sodi-Pallares[8] stated that the rate of conduction through the intramural muscle of the ventricular wall is not related to the thickness of the muscle but is rather a function of the greater or lesser penetration of the Purkinje network into the depths of the muscle. It has been pointed out[116, 117] that in the peripheral and particularly in the basal parts of the endocardium the Purkinje fiber may be relatively unbranched or sparse.

It has been suggested that in LVH the Purkinje network does not keep pace with the increasing thickness of the left ventricular wall and does not penetrate as deeply as in the normal, proportionately, so that more of the spread of activation is through the more slowly conducting muscle cells. Another possible cause of the delay in intraventricular conduction is that, with the left ventricular enlargement, there is spreading out of the Purkinje arborization. This results in a decrease in density of the Purkinje network per unit volume of muscle, and the impulse does not reach all regions of the endocardial surface quite so rapidly because it must travel through the enlarged fibers lying between the Purkinje junction.[88]

As the muscle fibers enlarge, they tend to outgrow their blood supply. The ratio of 1 capillary to 1 muscle fiber in the adult has been demonstrated to remain throughout life. Thus, in an enlarged heart there is a decrease in the number of capillaries per unit volume of myocardial tissue, which results in relative coronary insufficiency.[12, 62, 110] Some of the muscle fibers die and are replaced by fibrosis.[88] This replacement fibrosis of the myocardium may become quite marked. In such cases the excitation process may have to pursue a circuitous path around these areas of fibrosis. This results in a delay in the propagation and a resultant prolongation of the QRS.[88]

The mechanism of the production of the high-voltage changes encountered in LVH is even more speculative than that of the prolongation of the QRS complex just considered. As has been pointed out, with LVH there is an increase in the epicardial surface area of the left ventricle. This brings about an increase in the magnitude of the vectors generated during the period of epicardial excitation.[7, 33]

Increase in the solid angle subtended by the exploring electrode[88, 120] as a result of the increase in size of the left ventricle has been offered as a cause for the increase in potential recorded. Sodi-Pallares,[8] however, pointed out that the tracing depends on the number of dipoles enclosed by a given solid angle and that this angle is not altered by the presence of hypertrophy. He offered an explanation based upon the idea that activation spreads from the apex to the base of the heart with the wave front approaching the epicardium at a diagonal. Under these circumstances, an increase in thickness of the ventricular muscle results in a corresponding increase in the number of dipoles oriented to the electrode and the voltage of deflections recorded by the electrode is increased.

Still another explanation is that the free wall of the hypertrophied left ventricle is carried closer to the chest wall[8, 62, 88] and hence into closer proximity to the precordial electrodes. This position causes the exploring electrode to subtend a much wider angle, according to Barker,[88] and the potential variations recorded will be increased. Bayley[121] also observed that hypertrophy brings the ventricular muscle mass closer to certain precordial electrode positions. Such proximity of the heart in its volume conductor to the point under investigation tends to increase the magnitude of the potential variation. An additional factor in this connection is that there

may be a decrease in the volume of the poorly conducting lung between the heart and the chest wall.[62] Hypertrophy of the ventricular muscle also increases its area in relation to the area of short circuiting fluids surrounding the heart and contained in its cavities.[62]

Hypertrophy of the individual muscle fibers results in an increase in their cross sectional diameter. This change results in a decrease in the internal resistance while not altering the external resistance. This decrease in turn tends to increase the voltage generated by them on excitation.[20, 62, 88, 120]

A recent study, however, casts some doubt on this last hypothesis. Uhley[122] measured the transmembrane action potentials of the single cell in the hearts of normal control rats and in those with LVH secondary to induced hypertension. He found no significant difference in the cell potential between the 2 groups and concluded that increased voltage found in the electrocardiogram with LVH patterns is not the result of changes in single-cell generator amplitudes.

In the normal heart, the forces generated by the free wall of the left ventricle normally outlast those produced by the free wall of the right ventricle.[8, 81, 116, 117] The last portion of the left ventricle to be activated is the posterobasal region of the free wall.[7, 123] The terminal QRS forces therefore tend to be directed posteriorly and somewhat leftward.[7, 123]

In LVH the sequence of ventricular activation is the same as in the normal. In LVH it has been demonstrated by direct epicardial leads that there is delay in activation of the left ventricular surface, especially in the most basal and posterior regions.[124] This delay accounts for the posterior and superior deviation of the terminal vectors in LVH.[7, 33, 124] In other words, the ventricular activation in LVH is basically an exaggeration of the normal with the terminal forces having a more posterior and superior direction. The mean QRS vectors are increased in magnitude[33, 121] but not greatly altered in direction. The mean spatial QRS vector in LVH has the direction of a line from the center of the heart toward the free wall of the left ventricle.[121] This vector may or may not undergo a directional rotation.

Dilatation of the left ventricular chamber may occur alone or in combination with LVH. Dilatation tends to lengthen the endocardial pathway traversed by the excitation wave.[62] It also may result in further diminution of the density of the Purkinje fiber network. A further effect of dilatation may be to produce stretching of the conduction system, which reduces its cross sectional diameter and may cause direct mechanical injury resulting in a conduction disturbance.[62] Dilatation also produces an increase in the epicardial surface area of the left ventricle and the free wall is carried closer to the chest wall.[88] These features may result in QRS prolongation and increased amplitude.

Dilatation, however, results in an increase in the intracardiac blood volume, which acts as a shunt for the cardiac action currents and decreases the voltage of the electrocardiogram.[62] Congestive failure is a common accompaniment of left ventricular dilatation, and edema of the lungs also serves to short-circuit the flow of current in the cardiac field and decrease the voltage. Another possible cause for diminished voltage in left ventricular dilatation is the damage and destruction of muscle fibers that may be present. The net effect of dilatation upon the electrocardiographic pattern is therefore difficult to predict. Some workers[31, 33, 112] believed that the QRS changes attributed to LVH reflect only an increase in ventricular size whether due to hypertrophy, dilatation, or both. Barker[88] suggested, however, that left ventricular dilatation is seldom present without antecedent LVH.

Increase in the depth of the Q waves in leads overlying the left ventricle have been attributed to hypertrophy of the interventricular septum with increase in the electromotive forces appearing during its activation from left to right.[62, 88, 125] Grant,[7, 33] however, has presented evidence that casts some doubt upon the validity of the concept of a "septal Q wave."

The ST-segment and T-wave alterations

that occur in LVH may be secondary to the large QRS areas. It is thought that these alterations are related to the early onset of repolarization in the subendocardial region before activation has reached the epicardial surface.[88] It has been postulated[33] that the direction of repolarization in the normal heart is due to a gradient of pressure across the ventricular wall, the intramyocardial pressure being greater in the endocardial layers. Disappearance of this gradient in LVH has been offered as an explanation for the reversal of repolarization.[33] Objection, however,[121] has been raised to this latter explanation. Hypoxia of the endocardial layers, due to increasing intramyocardial pressure that opposes capillary blood flow, is thought not to be responsible for the direction of repolarization in the normal heart.[126] The role of the temperature gradient in the process of repolarization in the normal heart is still not clearly defined.[126] In these so-called secondary T-wave changes of LVH, the ventricular gradient is normal. In some cases of marked LVH the T-wave changes have also been considered to be secondary to a parietal wall conduction defect in the left ventricle.[33] Primary T-wave changes with an abnormally directed ventricular gradient may develop in LVH and are generally considered to be due to myocardial ischemia or coronary insufficiency.[33, 88, 121, 127]

It is probable that some tracings that have been regarded as characteristic of LVH are examples of incomplete LBBB.[8, 81, 121] Wilson[20] pointed out that incomplete LBBB can be excluded when there is a Q wave in one or more leads from the left precordium, but that the absence of Q waves is of no help. The electrocardiographic differentiation of incomplete LBBB from LVH may at times be difficult or impossible. Rasmussen and Moe[128] suggested that the electrocardiographic patterns in many patients with LVH are due to retarded conduction in the left heart. Grant and Dodge,[129] however, maintained that incomplete LBBB is exceedingly uncommon as a stable form of QRS prolongation.

The term left ventricular "strain" has become ambiguous. While some authors use the term synonymously with LVH,[16, 19, 130] others reserve it for the S-T depression and T-wave inversion in left ventricular leads without increased voltage of the R waves. Still others use the term "LVH and strain" when both high voltage of the R waves and the characteristic ST-T changes are present. Grant[33] stated that left ventricular strain should be diagnosed only when the S-T and T-vector changes are accompanied by increased magnitude of the QRS vector. Objection to the use of the term "strain" has been raised[20, 33, 121] on the grounds that the term is obscure, that it gives the connotation of a struggling weak heart about to fail, and that it introduces a mechanical term for an electrical phenomenon. Furthermore, similar S-T and T-wave changes may be caused by a multiplicity of factors, such as ischemia, digitalis, electrolyte alterations.[33, 131] Therefore, the term "strain" is not specific. As Kossmann[131] has pointed out, alterations in the S-T segment and T waves alone can scarcely be taken as indicative of anything anatomic.

Causes of False-Positive and False-Negative Diagnoses of Left Ventricular Hypertrophy

As has already been pointed out, the diagnosis of LVH can be reasonably accurately made from the clinical electrocardiogram. However, certain features must be taken into account and deserve emphasis. The age of the patient is important. In infants, children, and young adults, the voltage, particularly in the precordial leads, normally is greater than in older adults.[22, 33, 37, 131, 132] Therefore, different criteria for the amplitude of the QRS complexes must be employed for the various age groups. In infants and children the voltage criteria generally accepted for the diagnosis of LVH[38] exceed the maximum normal for their age.[37]

Grubschmidt and Sokolow[132] evaluated high voltage of the QRS (as defined by Sokolow and Lyon[22]) as the sole manifestation of LVH in a clinical study of 101 cases. They concluded that in adults over the age of 25, it is

reliable sign. However, in persons between 0 and 25 years, they stated that the sum of R in V_5 or V_6 and the S in V_1 should be considered high voltage only when it exceeds 40 mm. rather than 35 mm.

Aside from age, the individual's body build should be taken into consideration.[33] Thin-chested or emaciated individuals with normal hearts may have high voltage in the precordial leads that would ordinarily satisfy the criteria for LVH. Conversely, obese individuals or thick-chested individuals may have normal or even low-voltage QRS complexes, despite anatomic LVH.

Pathologic conditions such as myocardial infarction, congestive heart failure, pericardial effusion, pleural effusion, anasarca, and pulmonary emphysema may all serve to reduce the amplitude of QRS voltage in proved cases of LVH.

Of interest is the demonstration that administration of potassium salts to patients with hypertensive heart disease and LVH resulted in a reduction in the QRS voltage.[81, 133] Dietary restriction of sodium and sympathectomy[81] have also been shown to effect a reduction in QRS amplitude, which has not always been correlated with blood pressure reduction or change in heart size. These observations suggest that factors other than hypertrophy may contribute to the high voltage of the QRS complexes.[81]

Bryant[81] observed that incomplete LBBB may at times be confused with the pattern of LVH, or so-called left ventricular strain. He pointed out that the R wave in right chest leads and the Q wave in left chest leads may be absent or unusually small in some electrocardiograms that otherwise indicate LVH, and suggested that this may be due to incomplete LBBB. Conversely, some of the instances of false-positive diagnoses of LVH with delay in the onset of the intrinsicoid deflection[29] may, in fact, be examples of incomplete LBBB.

Certain cases of LVH show a discrepancy between the voltages in the limb and precordial leads. When the mean QRS vector is directed markedly posterior, its projection on the frontal plane is foreshortened, with the result that the limb leads exhibit normal or even low-voltage QRS complexes while the precordial leads have high voltage and a transition zone displaced to the left.[33] On the other hand, when the mean QRS vector is directed markedly leftward and parallel with the frontal plane, the transitional pathway for this vector passes through or near the precordial lead positions and small QRS complexes result while the limb leads display increased voltage of the QRS complexes.[33]

A false-positive diagnosis of LVH can occur with mitral insufficiency and a giant left atrium.[31, 33]

Right Ventricular Hypertrophy

In the normal adult heart the free wall of the left ventricle is approximately 3 times the thickness of the right ventricular wall. The normal electrocardiographic pattern is dominated largely by the activation of the left ventricle. When LVH occurs the result is ordinarily an accentuation of the normal configuration of the ventricular complexes.[88]

Lesser degrees of RVH produce no characteristic features in the electrocardiogram. In fact, the right ventricular wall may increase to double normal thickness, or even more, and still not produce sufficient increase in potential to counterbalance that produced by the normal free wall of the left ventricle.[88] Since only seldom in acquired heart disease does the thickness of the right ventricle equal and, even more rarely, exceed[62, 108] that of the left ventricle, it is perhaps even more surprising that the electrocardiographic diagnosis of RVH can be made with as much certainty as has been possible. In congenital heart disease the degree of RVH is usually more marked than in acquired RVH of the adult, and therefore ordinarily produces more marked electrocardiographic evidence of RVH.[33]

In the normal heart the right ventricle lies anteriorly to the left ventricle.[108] The plane of the interventricular septum is relatively parallel to the frontal plane of the body.[108] When RVH develops, there is an increase in the thickness of the free wall as well as an

increase in the epicardial surface area. As the hypertrophy progresses, the anterior surface of the right ventricle obliterates the retrosternal space and then comes to lie against the posterior aspect of the sternum and anterior chest wall. These rigid structures tend to limit any further forward enlargement of the right ventricle, so that any additional right ventricular enlargement must push the heart backward.[88]

With right ventricular hypertrophy there is also hypertrophy of the trabeculae carneae connecting the free wall of the right ventricle to the septal surface.[13, 108] Because of these hypertrophied trabeculae carneae the capacity of the hypertrophied right ventricle may not be significantly increased. With the onset of right ventricular dilatation, however, the trabeculae carneae network connecting the septum with the free wall becomes attenuated and appears to shift laterally. The capacity of the right ventricular chamber increases. This increase in effective inner surface area may be accomplished with little apparent change in outer contour of the heart.[108] Further enlargement of the right ventricle must take place by enlargement of the free wall because the septal surface is fixed by the size of the left ventricle. As dilatation continues, first the inflow and then the outflow tracts enlarge. With marked RVH and dilatation the right ventricle extends beyond the septal margin and the heart comes to have a "double apex."[108] Of particular interest is the observation that in some cases of RVH due to congenital heart disease there is an actual increase in the number of myocardial fibers due presumably to hyperplasia occurring during the first few months after birth. This is in contrast to the finding in acquired RVH in which there is no increase in the number of myocardial fiber units.[108]

Grant[33, 108] believed that when LVH is marked, RVH is a regular accompaniment. The explanation offered is that, since the interventricular septum consists almost entirely of left ventricular fibers, any increase in the size of the left ventricle automatically increases the septal surface of the right ventricle and, therefore, of the free wall of the right ventricle. Jones,[4] however, found in his autopsy study that in hypertension, in the absence of failure, only the left ventricle hypertrophies but with development of congestive failure, the right ventricle hypertrophies progressively with the duration of failure. Similar observations have been made by Fulton.[6]

The electrocardiographic patterns of RVH occur less frequently than do the patterns of LVH and are also subject to greater variation.[8] The QRS duration is not ordinarily prolonged because the pathway of activation through the right free wall is not, except in extreme RVH, as long as it is in the left free wall.[88] Activation of the right ventricle is normally completed in about 0.06 second or less. Therefore, a normal QRS of 0.09 would not become prolonged until marked RVH had developed. In fact, ordinarily in uncomplicated RVH, the QRS interval should not be prolonged beyond 0.10 second.[121]

The genesis of the increased voltage in the right precordial leads in RVH may be similar to that already discussed as causative in the high voltage in left ventricular leads in LVH. These factors include increase in thickness of the right ventricular wall, increase in the epicardial surface area of the right ventricle, proximity of the hypertrophied and often dilated right ventricle to the anterior chest wall, together with decrease in amount of intervening lung tissue, and decrease in internal resistance of the hypertrophied muscle fibers in the right ventricular wall.

The mean spatial QRS vector tends to increase in magnitude and to point more directly toward the hypertrophied free wall of the right ventricle.[121] Since the right ventricle lies anteriorly and slightly to the right of the left ventricle, the QRS forces developed from it normally are directed rightward and somewhat anteriorly.[33] When RVH develops these rightward and anteriorly directed forces are increased in magnitude. This change results in right axis deviation (RAD) of the mean QRS vector, which has been stated to be the most common manifestation of RVH.[33]

This mechanism presumably plays a prominent role in the RAD due to physiologic hypertrophy of the right ventricle in infants.[62]

It has been pointed out, however,[33] that the right ventricle normally contributes very little to the QRS complex and even marked RVH influences the direction of the mean QRS vector only slightly.[33] RVH results in marked RAD only in those subjects (children and young adults) where the mean QRS axis normally is more or less vertically directed. In older individuals whose normal mean QRS vector tends to be more horizontal, RVH much less commonly produces marked RAD.[33] Conduction delay in the right ventricle has also been implicated as a cause of RAD as it permits the electrical forces of the lateral wall of the right ventricle to be virtually unopposed by those of the left ventricle.[62] Dilatation of the right ventricle has been considered to cause clockwise rotation of the heart about its long axis and thereby also produces RAD.[62] Of course, Grant's studies[7] deny the importance of anatomic rotation of the heart in the genesis of the electrocardiographic pattern of RVH.

The anteriorly directed initial forces in RVH are responsible for the increased amplitude and duration of the R wave in the right precordial leads. When the terminal forces in RVH become anteriorly directed, there results an R′ in the right precordial leads. If the terminal vector is directed rightward and superiorly, with no prolongation of the QRS, the so-called S_1, S_2, S_3 syndrome is produced and is due to a conduction variation in the right ventricle.[33] If the terminal vector is inferiorly directed (as well as rightward and anteriorly) an S in lead I and an R′ in V_1 are present. As has already been discussed, this last pattern would be classed by many as IRBBB.

The S-T and T-wave alterations that may occur in the right precordial leads in RVH are generally considered to be secondary to the QRS abnormalities.[88] In marked RVH the S-T and T vectors are directed leftward and posteriorly,[33] opposite to the direction of the mean QRS vectors. Thus, the S-T segments tend to be depressed and the T waves inverted in leads II and III.

The precordial lead changes in RVH may be grouped into 4 main types, based principally upon changes in the right precordial leads.[8, 62] The first group displays tall R waves (with small or absent S waves) with late onset of the intrinsicoid deflection. It has been suggested that this pattern may be attributed to slow spread of excitation in the hypertrophied wall of the right ventricle.[62] Sodi-Pallares[8] attributed this type of pattern to clockwise rotation of the heart about its longitudinal axis, so that the thickened free wall of the right ventricle lies relatively close to the anterior chest wall. This type of pattern is commonly encountered in pulmonary stenosis and is due to concentric RVH.[134]

A second type also presents increased voltage of the R waves in V_1 but is preceded by a Q wave. The genesis of this qR pattern in right precordial leads in RVH has been and remains a somewhat confused problem. The proposed explanation[135] of marked clockwise rotation about the longitudinal axis, so that right precordial leads are facing the epicardial surface of the left ventricle, seems highly unlikely in view of Grant's studies.[7]

Initial depolarization of the interventricular septum from right to left in some of these cases has been suggested[102] and catheterization studies by Fowler and co-workers[136] would support this concept. Sodi-Pallares and associates[8] have offered another explanation for this pattern in RVH. They believe that the right atrium is markedly enlarged with the result that this dilated chamber transmits to the right precordial leads the electrical effects of vectors that originate in the high basal portions of the interventricular septum. These workers have studied at autopsy 42 cases that exhibited this pattern and found enlargement of the right atrium in all cases and concomitant hypertrophy or dilatation of the right ventricle in all but one.

Lepeschkin[62] has suggested that the Q wave corresponds to electrical forces, due to activation of the septum from right to left, which

are no longer opposed by those due to radial activation of the lateral wall of the right ventricle, as these appear later and are perhaps smaller due to decreased density of transitions between the conducting system and myocardium as a consequence of dilatation. Bayley[121] offered still another explanation for the Q wave in V_1 in RVH. He believed it was due primarily to apical activity of the right ventricle when its greater dimension and proximity to the xiphoid process creates a larger, negative solid angle at V_1 and V_2.

The third type of pattern that may occur is that of small r waves and deep S waves in the right precordial leads (and even in some cases in all precordial leads, including V_6). This pattern is encountered primarily in chronic cor pulmonale and is thought to be due principally to the anatomic position of the heart.[8] While the right ventricle is hypertrophied the heart is displaced downward in the chest owing to the low position of the diaphragm in pulmonary emphysema.[8] The QRS voltage is decreased because the precordial electrodes are relatively far removed from the ventricles.[8] Another explanation for this pattern is that there are right ventricular dilatation and clockwise rotation of the heart around its long axis displacing the rS pattern, which is thought to arise from the early right paraseptal ventricular region, to the left.[8, 62]

The fourth category is the rSR′ pattern in right precordial leads. This topic has already been discussed. Only a few additional points now need emphasis. This pattern, when it occurs in RVH, is ordinarily associated with right ventricular dilatation. This dilatation is thought to cause stretching and in some other way interfere with the right ventricular conducting network and result in a slowing of right ventricular conduction.

Grant[33, 134] has grouped the electrocardiographic changes in right ventricular enlargement into 3 main patterns and has formulated the concept that each of these depends upon the sequence in which the various regions of the right ventricle are activated during the QRS interval and whether right ventricular dilatation or hypertrophy is present. The septal portion of the right ventricle contributes its electric forces during the first 0.04 second of the QRS interval and the free wall of the right ventricle contributes its electric forces during the second half of the QRS interval.

1. When the septal and paraseptal portions of the right ventricle are involved in the hypertrophy, abnormal right ventricular forces are developed during the initial 0.04 second of the QRS interval. These forces are directed anteriorly and give rise to the abnormally tall and broad initial R waves in V_1. This pattern is encountered in pulmonic stenosis where there is concentric RVH.

2. When the inflow region of the free wall of the right ventricle (the portion that rests on the diaphragm) is predominantly hypertrophied or dilated, the terminal QRS forces point inferiorly and anteriorly. These produce right axis deviation in the standard leads and the transitional QRS complexes in the precordial leads are displaced to the right.

3. When the outflow portion and crista regions of the free wall are principally involved, the terminal forces point anteriorly and rightward. These produce an S wave in lead I and an R′ in V_1. This pattern is encountered in atrial septal defect where there is marked dilatation of the free wall of the right ventricle with sparing of the septal region. Grant believed that this RSR′ pattern in atrial septal defect was not IRBBB but a type of parietal block possibly due to fibrosis that is encountered in marked dilatation.

This neat distinction, based upon selective changes in the right ventricle as suggested by Grant, has to our knowledge not yet been subjected to careful correlation with autopsy and electrocardiographic studies.

The diagnosis of RVH in the presence of RBBB is fraught with considerable difficulty. The observations of Dodge and Grant[79] and of Fowler[89] have already been cited, as well as the autopsy study of Booth and associates.[95] In fact, Barker and Valencia[78] and Wilson[20] showed an illustration of intermittent complete RBBB in which the secondary R wave in V_1 was 15 mm. Yet, during normal

intraventricular conduction, there was no electrocardiographic evidence of RVH. Similar observations have been made by Levine.[137] Bryant[81] believed that if the activation of the free wall of the right ventricle was sufficiently delayed so as to follow the phase when the maximal forces were developed in the free wall of the left ventricle, that excitation of the right ventricular free wall alone might give rise to the relatively tall secondary R waves in the right precordial leads. He concluded that RVH in the presence of a major degree of IRBBB can be diagnosed from the electrocardiogram with little accuracy.

Combined Ventricular Hypertrophy

The electrocardiographic diagnosis of CVH is even more difficult than is the diagnosis of isolated or preponderant hypertrophy of either ventricle. Normally the free wall of the left ventricle is approximately 3 times the thickness and twice the weight of the free wall of the right ventricle. If both ventricles undergo hypertrophy, but retain their relative proportions to each other, the left ventricle remains preponderant and the electrocardiogram tends to display the pattern of left ventricular hypertrophy.[88] In fact, Wilson[20] doubted that hypertrophy which increases the masses of the 2 ventricles proportionately could be distinguished from preponderant hypertrophy of the left ventricle alone. In addition, the observation has been made that even in RVH the thickness of the right ventricular wall seldom approaches, and only rarely exceeds, the thickness of even the normal left ventricular wall and that it seems unlikely that when the left ventricle is greatly hypertrophied even the most marked RVH could significantly alter the QRS forces.[33]

It is an observed fact, however, that biventricular hypertrophy does, on occasion, give rise to highly suggestive, if not absolutely diagnostic, patterns. Barker[88] believed that in order to produce an electrocardiographic pattern of CVH there must be increased thickness of the free wall of the left and of the right ventricle to almost equal degree. The QRS interval may be normal[19] or slightly prolonged in CVH.[88] The prolongation is presumably due to the increased time required for the impulse to spread through the thickened portion of the free wall of the left ventricle. Since the increased voltages generated by the hypertrophied ventricles tend to counterbalance each other, the amplitude of the deflections in the electrocardiogram may not greatly exceed the normal. There may be S-T and T-wave changes secondary to the increased duration of the QRS interval. Slurring and notching of the QRS complexes may occur because of local delays in intraventricular conduction due to widespread myocardial fibrosis.

Many patterns purported to be of value in the diagnosis of CVH have been offered.[19, 62, 96, 97] Among the more useful are the presence of LVH in the precordial leads with a vertical heart (or right axis deviation $>+90°$); marked displacement of the transitional zone to the left with S>R in V_5, R>Q in aV_R together with signs of LVH; tall R waves with late peaks and inverted T waves in both right and left precordial leads.

Dilatation of the right ventricle in bilateral ventricular enlargement has been invoked to explain the displacement of the transition zone to the left, with "clockwise" rotation of the heart producing right axis deviation.[62] It has been suggested that such "clockwise" rotation does not occur when the right ventricular enlargement is subsequent to left ventricular failure, for in these cases the right ventricle expands upward without displacement of the dilated left ventricle backward.[62] When in combined ventricular enlargement there is more hypertrophy than dilatation of the right ventricle, the pattern of increase in voltage in the right precordial leads is encountered.[62]

The electrocardiographic pattern encountered in ostium primum defects (persistent common atrioventricular canal) is of interest. There is LAD in the standard leads (especially of the initial forces) and an rSR′ pattern in the right precordial leads.[8, 33, 38, 66, 134, 138-140] The left precordial leads may also display evidence of LVH,

While it has been proposed that the LAD is due to the associated mitral insufficiency (resulting from the cleft mitral valve),[138, 140] others deny this and attribute this configuration to altered spread of conduction through the left ventricle.[33, 134, 139] At autopsy these cases exhibit RVH and dilatation and may also show LVH.[38, 141]

Since the introduction of the concept of ventricular overload,[77] patterns of CVH, especially in congenital heart disease, have been described. These patterns are further considered in the section on ventricular overload syndromes.

Ventricular Overload Syndromes

The interesting concept of systolic and diastolic overloading of the heart was introduced by Cabrera and Monroy[77] and extended by Sodi-Pallares.[8, 66, 142, 143] They have described what they believe are specific electrocardiographic features and have related them to characteristic anatomic alterations in the ventricles. Systolic overloading of the right ventricle is illustrated by cases of pulmonic stenosis and of pulmonary hypertension. The electrocardiogram displays an increase in voltage of the R waves in right precordial leads and (in advanced cases) T-wave inversion. At autopsy these cases are found to have thickening of the free wall of the right ventricle and slight or moderate dilatation of the outflow tract only.

Diastolic overloading of the right ventricle is illustrated by atrial septal defect and by tricuspid insufficiency. The electrocardiogram exhibits RBBB (complete or incomplete) and at autopsy there is dilatation of the right ventricle. The stretching of the conducting fibers and increase in length of the conduction pathway associated with dilatation have been considered as causative factors in the production of the electrocardiographic pattern.

Systolic overloading of the left ventricle is found in aortic stenosis and in systemic hypertension. The electrocardiographic pattern is characterized by ST-segment depression and T-wave inversion in left ventricular leads. At autopsy these cases display a thick-walled left ventricle without significant dilatation of the cavity. Cabrera and Monroy[77] regard these T-wave changes as "primary."

Diastolic overloading of the left ventricle occurs in aortic insufficiency and in patent ductus arteriosus. The electrocardiographic pattern is characterized by tall R waves with late peaks in left precordial leads and deep S waves in right precordial leads. The T waves are tall and peaked[8, 66] and may be preceded by an upward S-T displacement in the left precordial leads. At autopsy there is usually considerable dilatation of the left ventricular cavity, with slight thickening of the wall.

Systolic overload is thought to manifest itself principally at the time of ventricular repolarization. The effect then is to delay the onset of repolarization, with the T waves of the affected ventricle becoming flattened or negative. Diastolic overload lengthens the activation process of the involved ventricle. The electrocardiogram shows a delay in the onset of the intrinsicoid deflection in the precordial leads reflecting the involved ventricle.

Combined right and left ventricular overload patterns have been described in a variety of congenital heart conditions.[8, 72, 73, 142, 143] Marsico and Sodi-Pallares[142, 143] found this electrocardiographic pattern in 56 per cent of their 32 cases of ventricular septal defect. These cases exhibited (1) RVH with systolic overloading of the right ventricle with tall R waves in V_1 and V_2; (2) LVH with or without diastolic overloading of the left ventricle characterized in V_5 and V_6 by tall or normal R waves when a small deflection would be expected due to the marked RVH, delayed onset of the intrinsicoid deflection, positive T waves; (3) deep Q waves in V_5 and V_6, suggestive of septal hypertrophy. The mean spatial QRS vector deviated to the right, forward, and upward.

Patent ductus arteriosus with moderate pulmonary hypertension also has been shown to demonstrate CVH, characterized by RVH with systolic overloading and left ventricular diastolic overloading with tall peaked T waves in V_5 and V_6.[8, 143] Ziegler[72, 73] has also de-

scribed what he considers several diagnostic patterns of CVH in infants, characterized by various combinations of right and left ventricular overload patterns. He has pointed out that in infancy with QRS or T evidence of RVH in right precordial leads, the occurrence of T-wave inversion in left precordial leads is strong presumptive evidence of associated LVH. Another observation made by Ziegler[73] was that in infants with electrocardiographic evidence of LVH the presence of positive T waves in right precordial leads is evidence of probable RVH, if the R in V_1 exceeds 40 to 50 per cent of the total amplitude of RS in that lead. Some of Ziegler's observations have been supported by anatomic studies.[73]

The concept of systolic and diastolic overloading of the ventricles has been of considerable value in the interpretation and evaluation of the electrocardiogram in various forms of congenital heart disease.[8, 66, 72, 73, 77, 142, 143] However, to our knowledge there have been no extensive, careful, autopsy-controlled correlations with these electrocardiographic patterns. In fact, such an evaluation might be difficult because the concept of systolic and diastolic overload implies a physiologic or hemodynamic, more than an anatomic, alteration in the ventricles. Nevertheless, certain empiric observations have been made. In general, when ventricular enlargement is due to increased flow (diastolic overload), there is ventricular dilatation, and when the enlargement is due to increased resistance to flow (systolic overload), there is ventricular hypertrophy.[33] It has also been observed that in congenital heart disease dilatation is more often accompanied by minor conduction defects than is hypertrophy, especially in the right ventricle. Left ventricular dilatation is said to increase QRS amplitude, whereas LVH is prone to produce accompanying S-T and T-wave changes.[33] The recent study of Selzer and associates,[35] however, tends to discount the distinguishing electrocardiographic features between LVH and left ventricular dilatation. The right ventricular diastolic overload pattern, so commonly encountered in atrial septal defect, has been shown post mortem to be associated with right ventricular dilatation;[8] no relationship could be detected between the RBBB and the thickness of the septum or the right ventricular wall. Objection has been raised to the concept of the overload syndrome in that the electrocardiogram cannot record hemodynamic or mechanical events but only those anatomic and conduction alterations that may accompany such changes.[33, 121, 144] Kossmann[131] has pointed out that minor degrees of LBBB may be causative in the production of the electrocardiographic pattern of so-called left ventricular systolic overload. Therefore, the whole problem of the overload syndrome, while of considerable clinical interest, is not necessarily on a firm structural basis. Sodi-Pallares,[66] furthermore, admits that there are diagnostic limitations to these electrocardiographic patterns.

Discussion

It would appear that with the considerable uncertainty still surrounding the exact mode of production of the electrocardiographic phenomena in ventricular hypertrophy, any attempt to correlate largely empiric electrocardiographic patterns with the anatomic expression of this hypertrophy may well lead not infrequently to evidence of disparity in the results. Furthermore, it has been pointed out[20, 37] that in indirect leads, there is no necessary correlation between the amplitude or duration of the QRS complex and the magnitude of the transmural voltage or the thickness of the ventricular wall. The QRS deflections represent the net effect of two sets of electric forces (opposite in sign) generated, not only in the portion of the heart immediately underlying the exploring electrode, but in all other parts of the heart as well.[20] In addition, it has been emphasized[37] that because of the composite value of the ventricular deflections in semi-direct leads, it is difficult, or perhaps impossible, to ascribe to a precise portion of the electrocardiogram electrical activity arising in an equally precise area of the right ventricle or left ventricle.

Despite the problems inherent in such stud-

ies, certain significant facts emerge. With the use of conventional electrocardiographic criteria for the diagnosis of LVH in adults an accurate diagnosis in autopsy-proved instances of isolated LVH is possible in about 85 per cent.[27] On the other hand, given an electrocardiogram demonstrating the pattern of LVH in an adult, the possibility of making a false-positive diagnosis ranges from about 10 per cent to 15 per cent.[28, 29] This is at variance with the experience of Levine and Phillips,[26] who found that LVH was invariably present at autopsy when diagnosed electrocardiographically.

Emaciation, slender body build, and age appear to be some of the major factors resulting in a false-positive diagnosis of LVH. Obesity has been shown in some cases to obscure the electrocardiographic diagnosis of LVH. Thus the voltage criteria in LVH may be totally unreliable in subjects who are either markedly overweight or underweight. In addition, the present voltage criteria for LVH in adults may result in overdiagnosis in children and even in some normal young adults. Generally speaking, minimal or early LVH is more likely to be missed than is marked LVH.

Of the various groups of electrocardiographic criteria for the diagnosis of LVH, delay in the onset of the intrinsicoid deflection was considered by Selzer to be the least reliable, having been present in many cases without anatomic LVH and absent in some with severe hypertrophy.[29] In our study of autopsy-proved isolated LVH, delayed ventricular activation time was encountered in 26 per cent of the cases.[27] Increase in voltage was present in 29 per cent of cases of isolated LVH.[27] In Grant's series[31] high voltage occurred in over 90 per cent of cases with marked LVH. Selzer[29] found high voltage to be present in most cases in his series but in that study the tracings were selected because they displayed LVH. He also found high voltage to be the most frequent cause of a false-positive diagnosis of LVH.

No close relationship can be demonstrated between any specific electrocardiographic abnormality and the ventricular weight, the left ventricular wall thickness, or the LV/RV wall thickness ratio. However, a significant association was found between increasing heart weight and increasing accuracy of diagnosis.[27]

The accuracy of electrocardiographic diagnosis of autopsy-proved preponderant or isolated RVH in different series varies widely (23 to 100 per cent). These reports, however, include heterogeneous groups with wide age ranges, varied etiologies of the RVH, and the utilization of various electrocardiographic criteria. To attempt to achieve some semblance of order from these studies, it may be observed that the electrocardiographic diagnosis of RVH is most accurate in congenital heart disease, less so in mitral stenosis and chronic cor pulmonale, and commonly undetected in RVH secondary to left heart failure. In most instances when the pattern of RVH is encountered in the electrocardiogram, the diagnosis is substantiated at autopsy, yet Walker and associates[50] found that 4 of 12 patients presenting this pattern did not have RVH at autopsy. Lipsett and Zinn[97] also found 5 of 17 cases with anatomic LVH to exhibit electrocardiographic evidence of RVH.

Anatomic CVH may present any of the following electrocardiographic patterns: (1) normal, (2) nonspecific abnormalities, (3) bundle-branch block, (4) preponderant hypertrophy of 1 ventricle, usually the left, or (5) a diagnostic pattern of biventricular hypertrophy. While a vertical axis in the presence of electrocardiographic evidence of LVH in the precordial leads has been proposed as highly suggestive of CVH, yet this pattern has been occasionally encountered in LVH alone.

Delay in the onset of the intrinsicoid deflection in right precordial leads in RVH and in left precordial leads in LVH has constituted an integral part of the conventional criteria in the electrocardiographic diagnosis of ventricular hypertrophy.[20, 22, 42, 43] However, there has been increasing skepticism concerning the significance of the intrinsicoid deflection. This has stemmed largely from vectorcardiographic studies.[44, 145-147] Milnor,[44] in

act, stated that he does not make measurements of the "intrinsicoid deflection" because ie believes that they are misleading in theory nd of no value in practice. As he pointed ut,[44] it is probable that no precise meaning eferable to a localized area of the myocarlium can be assigned to the "intrinsicoid leflection." Actually, Wilson himself emphaized that the potential variations of every lement of the epicardial surface contribute n some measure to the potential variations of n electrode placed upon the precordium.[148] Therefore, although the exact significance and importance of the intrinsicoid deflection is at he present time still uncertain, it is an empiric observation that the onset is delayed in at least some cases of ventricular hypertrophy.

The value of axis deviation in the diagnosis of ventricular hypertrophy has undergone cycles of waxing and waning popularity. When the standard leads constituted the mainstay of electrocardiographic leads, right axis deviation (RAD) and left axis deviation (LAD) were given considerable importance in the diagnosis of respective ventricular hypertrophy. With the introduction of the unipolar extremity and chest leads, the importance attached to axis deviation diminished. In fact, Myers[42] and Braunwald[40] have indicated that axis deviation is of little or no value in the diagnosis of ventricular hypertrophy. Kossmann[135] has stated that it is doubtful that RVH, except on rare occasions, can cause RAD by itself.

However, with the considerable interest at present in vectorcardiography and vectorelectrocardiography, the evaluation of the frontal plane projection of the mean QRS axis in the scalar electrocardiogram has again gained favor. Milnor[44] has placed considerable emphasis on RAD in the diagnosis of RVH. Phillips[53] has demonstrated that RAD occurs earlier than the changes in the right precordial leads in the development of RVH in cor pulmonale. Grant[33] has stated that RAD is the commonest manifestation of RVH. The relationship of LAD to LVH is perhaps somewhat less specific. Grant's studies of LAD in LVH have already been cited, including his belief that it is not the hypertrophy itself that produces the axis deviation but a conduction defect in the left ventricle.[31–33] In our present state of knowledge, it would appear that abnormal degrees of axis deviation are of importance in the electrocardiographic evaluation of ventricular hypertrophy and, therefore, axis deviation should be determined.

That errors may occur in the electrocardiographic diagnosis of ventricular hypertrophy are well recognized and have been emphasized by Kossmann.[135, 149] The lack of agreement among various authorities in the electrocardiographic diagnosis of LVH has been specifically pointed out by Dimond.[150]

It would appear appropriate to speculate about the possibility of future improvements in the electrocardiographic diagnosis of ventricular hypertrophy. Perhaps some of the proposed orthogonal electrocardiographic lead systems[151, 152] may simplify the electrocardiographic criteria and improve the diagnostic accuracy. Again, however, only an electrocardiographic-pathologic evaluation of such systems will establish their merit in this regard.

Summary

The correlation of the electrocardiogram with anatomic evidence of ventricular hypertrophy, while laden with numerous pitfalls, still remains the best available means of determining the accuracy of the electrocardiographic diagnosis of ventricular hypertrophy.

In 100 instances of isolated left ventricular hypertrophy (LVH) demonstrated at autopsy, a positive electrocardiographic diagnosis was made in 85 per cent by use of conventional criteria. However, in other studies designed to test the reliability of these criteria, it was found that a false-positive diagnosis was made in 10 to 15 per cent of the cases.

The electrocardiographic diagnosis of right ventricular hypertrophy (RVH) is more difficult. In electrocardiographic studies, confirmed by autopsies, the correlation has ranged from 23 to 100 per cent, while the number of false-positive diagnoses has been as high as 33 per cent. The correct electrocardiographic diagnosis is more frequent in

RVH due to congenital heart disease than to acquired heart disease.

The significance of the rSR′ pattern in right precordial leads is discussed. Its occurrence in anatomic RVH and the problem of the electrocardiographic diagnosis of RVH in the presence of right bundle-branch block (RBBB) are reviewed.

Combined ventricular hypertrophy (CVH) is frequently missed in the electrocardiogram, the diagnosis having been made in only 8 to 26 per cent of cases proved at autopsy.

The unreliability of the electrocardiographic diagnosis of LVH in the presence of left bundle-branch block (LBBB) is documented.

The precise electrophysiologic phenomena that occur in ventricular hypertrophy are still largely conjectural. The more commonly accepted hypotheses are reviewed.

The lack of close correlation between ventricular wall thickness or respective ventricular muscle mass and the individual electrocardiographic patterns is emphasized. The possible explanations for some of these discrepancies are presented.

Summario in Interlingua

Le correlation del electrocardiogramma con evidentia anatomic de hypertrophia ventricular curre le risco de numerose fallacias, sed illo remane nonobstante le melior medio disponibile pro determinar le accuratia del diagnose electrocardiographic de hypertrophia ventricular.

In 100 casos de isolate hypertrophia sinistro-ventricular (HSV) demonstrate al necropsia, un positive diagnose electrocardiographic esseva facite 85 pro cento del vices per le application del criterios conventional. Tamen, in altere studios planate pro testar le fidelitate de ille criterios, il esseva trovate que un diagnose false-positive habeva essite facite in inter 10 e 15 pro cento del casos.

Le diagnose electrocardiographic de hypertrophia dextero-ventricular (HDV) es plus difficile. In studios electrocardiographic, necropticamente confirmate, le correlation ha variate inter 23 e 100 pro cento, e le numero del diagnoses false-positive ha essite alte, usque a 33 pro cento. Correcte diagnoses electrocardiographic de HDV es plus frequente quando le condition es le effecto de congenite morbo cardiac que quando illo es le effecto de acquirite morbo cardiac.

Le signification del patrono rSR′ in derivationes dextero-precordial es discutite. Es revistate su occurrentia in HDV anatomic e etiam le problema del diagnose de HDV in le presentia de bloco de branca dextere.

Hypertrophia ambi-ventricular (HAV) escappa frequentemente al examine electrocardiographic. Le diagnose esseva facite in solmente 8 inter 26 casos in que le condition esseva provate al necropsia.

Le basse fidelitate del diagnose electrocardiographic de HSV in le presentia de bloco de branca sinistre es documentate.

Le precise phenomenos electrophysiologic que occurre in hypertrophia ventricular remane in grande mesura conjectural. Le theorias le plus commun mente acceptate es revistate.

Es signalate le manco de correlation inter le spissitate del pariete ventricular o le respective massa muscular e le configuration electrocardiographic in caso individual. Es presentate explicationes possibile pro certes de iste discrepantias.

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Barker, W. F.: The Management of Venous Thrombosis and Pulmonary Embolism. Surgery **45**: 198 (Feb.), 1959.

The treatment of established venous thrombosis and pulmonary embolism remains a problem. A survey of 80 cases of deep venous thrombosis treated by anticoagulants indicated a serious failure rate in the form either of recurrent venous thrombosis or of originally occurrent or recurrent pulmonary embolism. Heparin was more effective than Dicumarol in relieving symptoms of venous thrombosis, but was associated with a number of fatal pulmonary emboli in the presence of apparently adequate therapy. Venous ligation, especially at the level of the vena cava, supplemented by postoperative anticoagulant therapy seemed to offer the safest course with minimal morbidity.

KITCHELL

ABSTRACTS

ELECTROCARDIOGRAPHY, VECTORCARDIOGRAPHY, BALLISTOCARDIOGRAPHY, AND OTHER GRAPHIC TECHNICS

Daoud, G., Reppert, E. H., Jr., and Butterworth, J. S.: Basal Systolic Murmurs and the Carotid Pulse Curve in the Diagnosis of Calcareous Aortic Stenosis. Ann. Int. Med. **50**: 323 (Feb.), 1959.

The clinical diagnosis of calcareous aortic stenosis is difficult to establish. In a group of 30 patients with proved aortic stenosis at autopsy, the clinical diagnosis was made in only 35 per cent. The authors reviewed the physical and laboratory features of calcareous aortic stenosis and indicated the variability in each finding. The blood pressure usually revealed a low systolic level and a low pulse pressure, but hypertension and wide pulse pressures occurred. Although left ventricular hypertrophy was the most common electrocardiographic finding, distortions of this pattern by antecedent myocardial infarction or conduction disturbances were sometimes found. The limitations of the x-ray, fluoroscopic examinations, auscultation, and phonocardiogram were also reviewed. The carotid pulse wave was recorded by a neck cuff attached by a thin-boro rigid-wall plastic tubing to a Statham strain-gage transducer. The output of the transducer was amplified by a carrier-wave amplifier and fed to an optical galvanometer and recorded on photographic paper. The features of the carotid pulse wave in patients with aortic stenosis include a rapid rise in the ascending limb, an inconstant anacrotic notch, and a variable plateau, interrupted by the incisura. Two angles in the curves were also measured. The angle E, or ejection angle, was formed by the perpendicular at the beginning of the systolic upstroke and a line tangent to the initial rise of the upstroke. The S angle, or systolic angle, was formed by the tangent line of angle E and a line drawn from the origin of the upstroke to the incisura. In 25 normal subjects and in 150 patients without aortic stenosis, angle E varied between 6° and 25°, with 1 exception. Angle S was always larger than E, with 1 exception, and the ratio E/S was always less than 1. In 40 patients thought to have calcareous aortic stenosis, the carotid pulse curve revealed a slow rise of the ascending limb, small to absent incisura, and diminished over-all height of the curve. The ejection angle E was above 25°, (usually above 30°) and the systolic angle S was decreased, so that E/S was greater than 1, with 3 exceptions. In general, the systolic time was greater than 0.24 second. A classification of severe aortic stenosis, aortic stenosis, and nonhemodynamic aortic stenosis is given with the clinical and laboratory features of each group.

KAYDEN

Deglaude, L., and Laurens, P.: Contribution of the Vectorcardiogram to the Recognition of Combined Ventricular Overload. Arch. mal. coeur **52**: 263 (Mar.), 1959.

In systolic or pressure overload the QRS loop is directed to the right, anteriorly, and downward in the case of the right ventricle, and to the left, posteriorly, and upward in the case of the left ventricle. The T loop is displaced in an opposite direction and has high voltage. In diastolic or volume overload the changes are similar except

that the QRS loop has an irregular course and longer duration, and the T loop shows low voltage. The delay of QRS is especially pronounced if the opposite ventricle shows systolic overload. In this instance the initial portion of QRS often deviates in a direction characteristic for right ventricular overload, the terminal portion in that characteristic for left. The electrocardiogram in such cases often shows a biphasic QRS complex or contradictory limb and precordial leads. Less commonly, bilateral overload leads to complete neutralization of the effects of both ventricles, so that the loops appear normal, or they show overload of a lesser degree than would correspond to the actually observed right ventricular pressures.

LEPESCHKIN

Duboucher, G., and Bernasconi, P.: Ventricular Paroxysmal Tachycardia of the Bouveret Type, Showing Evolution after Twelve years. Arch. mal. coeur **52**: 55 (Jan.), 1959.

An otherwise healthy male experienced his first episode of paroxysmal ventricular tachycardia at the age of 39. At this time the rate of the ectopic center was 140 and frequent atrial captures were present. During the following 10 years the episodes became more frequent and prolonged, and the ventricular rate sometimes reached 200. The attacks always could be interrupted by slow intravenous injection of 6-8 ml. of pronestyl, which caused a progressive slowing of the ventricular pacemaker without influencing the atrial rate; the attack ceased suddenly as soon as the ventricular rate slowed down to about 135. For 1 to 2 weeks after cessation of the attack the T wave was inverted in leads II and III; after longer attacks the T wave usually became inverted also in leads V_{1-6} and became normal less rapidly. The axis of the abnormal post-tachycardia T waves was identical with the QRS axis of the ectopic rhythm, making it probable that both were localized to the posterior wall of the ventricle, and were probably caused by functional coronary insufficiency in this region. This conclusion was corroborated by the observation that as long as the T-wave changes were present the heart was enlarged and the posterior wall showed reduced amplitude of pulsation.

LEPESCHKIN

Garrarienti, F., and Lapiccirella, R.: Observations on Certain Phonocardiographic Tracings in Patients with Mitral Disease. Arch. mal. coeur **52**: 46 (Jan.), 1959.

The illustrated phonocardiograms show that the typical presystolic murmur of mitral stenosis disappears with the disappearance of P waves in atrial fibrillation, and that in progressive increase of the P-R interval this murmur becomes separated from the first heart sound but retains its temporal relations to the P wave. These observations are contrary to the recently advanced concept that the presystolic murmur is caused by ventricular contraction.

LEPESCHKIN

Hon, E. H.: Observations on "Pathologic" Fetal Bradycardia. Am. J. Obst. & Gynec. **77**: 1084 (May), 1959.

Observations based on 500 fetal electrocardiographic tracings are discussed. The transitory V-shaped bradycardia associated with uterine contractions and increased intracranial pressure has a different pattern from the U-shaped pathologic bradycardia. If the bradycardia began toward the end of the contraction, it appeared to be more serious than a bradycardia that was confined to the contraction period. If the pathologic U-shaped pattern was progressively widening and the return to normal was associated with irregularity, it was considered evidence that the condition of the fetus was slowly growing worse. The author presents a hypothesis to explain the fetal bradycardia noted in abnormal labor. He relates the bradycardia to hypoxia secondary to alteration in the blood flow in the intervillous space. This latter is related to a normal differential between intramyometrial and maternal blood pressure, as well as sufficient relaxation between uterine contractions. It was also noted that transitory tachycardia of 170 to 180 beats per minute followed some episodes of bradycardia and irregularity. This is said to be the result of lesser degrees of hypoxia.

SHEPS

Larks, S. D.: The Fetal Electrocardiogram in Multiple Pregnancy. Am. J. Obst. & Gynec. **77**: 1109 (May), 1959.

Electrocardiographic recordings from twins, triplets, and quadruplets are presented. The diagnosis of multiple pregnancy by the fetal electrocardiogram is demonstrated. The fetal electrocardiogram is suggested as an alternate method of diagnosis when x-ray technic may not be desired. The diagnosis of a twin pregnancy at 16 weeks is presented.

SHEPS

Laurens, P., Bouchard, P., Brial, E., Cornu, C., Baculard, P., and Soulié, P.: Cardiovascular Sounds and Pressures Registered In Situ by Means of a Micromanometer. Arch. mal. coeur **52**: 121 (Feb.), 1959.

The head of the pressure transducer, which

operates on a frequency modulation principle, is 2.6 mm. wide and 8 mm. long, and is situated at the tip of a double-lumen 8-F catheter having a side opening through which blood samples can be taken. The frequency response of the manometer is 0 to 5,000 c.p.s., and enables registration of pressures or vibrations without delay or distortion through damping or resonant vibration. Comparison with tracings registered by means of an ordinary manometer through the side opening shows that the latter have a delay of 0.01 to 0.03 second. Study of 70 patients with the micromanometer showed that murmurs were registered only at the site of the pressure gradient and in the immediately adjacent region downstream. Thus, the murmur of tricuspid regurgitation was registered only in the right atrium, that of tricuspid stenosis only in the right ventricle, that of pulmonic stenosis only in the pulmonary artery. In atrial septal defect the systolic murmur was registered only in the pulmonary artery and was therefore caused by relative pulmonary stenosis: in contrast to true pulmonary stenosis, it was of low amplitude and had a frequency of less than 130 c.p.s. In pulmonary stenosis the murmur had about equal amplitude in the entire pulmonary trunk, but had much higher frequency components in the region of the stenosis. In aneurysm of a sinus of Valsalva, perforated into the right ventricle, a diastolic murmur could be registered in the right ventricle, whereas this was not possible in aorticopulmonary or interventricular communications.

LEPESCHKIN

Lewis, D. H., Ertugrul, A., Dietz, G. W., Wallace, J. D., Brown, J. R., Jr., and Moghadam, A. N.: Intracardiac Phonocardiography in the Diagnosis of Congenital Heart Disease. Pediatrics **23:** 837 (May), 1959.

Intracardiac phonocardiograms were obtained from 63 patients with congenital heart disease and from 11 pediatric patients without heart disease. The degree of localization of heart sounds and murmurs on the surface of the thorax was much less than that within the heart. The intracardiac phonocardiogram proved to be of great value in studying and localizing valvular lesions and left-to-right shunts. The authors point out that blood itself provided a certain amount of acoustic damping which was circumvented by the use of intracardiac phonocardiography.

KARPMAN

Mouquin, M., Brun, P., Chartrain, E., Allain and Pelletier, D.: Chronic Constrictive Pericarditis and Catheterization of Both Ventricles. Arch. mal. coeur **52:** 123 (Feb.) 1959.

Left ventricular catheterization with a polyethylene catheter containing a removable steel wire with an elastic end, introduced through the femoral artery, was executed in 66 patients and successful in 52; the only complications were infections easily controlled by antibiotics in 3 patients. In persons without pericarditis a protodiastolic dip followed by a diastolic plateau was seen only if the diastolic pressure was less than 5 mm. Hg. In patients with constrictive pericarditis the dip was present at a diastolic pressure of about 10 mm. In 2 of the patients the same finding was present also in the right ventricle, catheterized simultaneously from the cubital vein. This finding permits the recognition of a pericardial constriction extending also to the left ventricle.

LEPESCHKIN

Ross, J., Jr.: Transeptal Left Heart Catheterization. A New Method of Left Atrial Puncture. Ann. Surg. **149:** 395 (Mar.), 1959.

A method of catheterizing the right and left hearts simultaneously in dogs is described. A catheter was passed into the femoral vein and then into the right side of the heart. After pressure readings were made with the catheter in the right atrium, a needle was passed through the interatrial septum into the left atrium. Through this needle, small plastic catheters could be passed into the left ventricle and even into the aorta. This procedure was carried out in 37 dogs, 26 normal, 10 with experimentally produced mitral insufficiency and 1 with a congenital ventricular septal defect. Entry into the left atrium is easily detected by a change in resistance and difference in color of the blood. The tracings of the right and left atrial pressures revealed characteristically different pulse contours in all instances No serious arrhythmias were encountered. Left atrial angiograms were performed in 9 dogs. The dog with the congenital ventricular septal defect died the night following the angiocardiography. There was gross pulmonary edema post mortem. Another dog, dying after this procedure, exhibited no apparent cause of death. In 2 dogs the interatrial puncture site was still patent at operation 7½ weeks and 3½ months after the procedure. Accidental entry into the pericardium, or perforation of the aorta or left ventricle was not encountered. In man the greater size of the interatrial septum and the lesser mobility of the mediastinum should facilitate entry into the left atrium and render even less likely the possibility of a misplaced puncture. This procedure may be worthwhile clinically in infants and small children where left heart catheterization may be difficult by

transbronchial or percutaneous method. In adults, where the transbronchial and percutaneous methods fail, this procedure could be used. Preliminary studies in human cadavers indicate that with minor modification this technic is applicable.

LEVINSON

Saracoglu, K.: Electrocardiographic Changes Registered During Agony and after Clinical Death. Arch. mal. coeur **52**: 313 (Mar.), 1959.

In 30 personally observed cases electrical activity of the heart always ceased 1 to 40 minutes after clinical death. The last activity to be registered was usually ventricular fibrillation in patients who died of heart disease, while in those dying from other causes normal sequence of activation may persist, with depression or elevation of S-T and sometimes extreme shortening of Q-Te. In many cases the amplitude of the electrocardiogram is normal at a time when all mechanical activity has disappeared.

LEPESCHKIN

Silver, A. M., Siderides, L. E., and Antonius, N. A.: The Right Precordial Leads in Congenital Heart Diseases Manifesting Right Ventricular Preponderance. Am. J. Cardiol. **3**: 713 (June), 1959.

The QRS morphology of lead V_1 was examined along with the right ventricular pressure in 91 congenital heart patients. Of 13 patients having atrial septal defect, all had an rsR′ pattern (diastolic overloading) excepting 2 with moderate right ventricular hypertension who presented qR patterns. Dominant R patterns of similar varieties (systolic overloading) were found in 14 instances of pulmonary stenosis with atrial septal defect, 28 of tetralogy of Fallot, and in 32 of 36 of isolated pulmonary stenosis. Eighteen per cent of the systolic overloading group showed rsR′ complexes, the initial r of which was less than 0.025 second in duration. The 4 instances of dominant S waves in pulmonary stenosis occurred in association with right ventricular systolic pressures of 38 mm. Hg or lower. rsR′ patterns with initial r waves over 0.025 second in duration were thought to represent a disturbance in activation of the right ventricle occurring when its volume work was increased. rsR′ with abbreviated initial r waves, qR′, or notched R waves appeared to indicate hypertrophy of the crista supraventricularis. Tall R or Rs tracings were believed to be due to hypertrophy of the free ventricular wall.

ROGERS

Sodi-Pallares, D., Bisteni, A., Fishleder, B. L., and Medrano, G. A.: Importance of the Unipolar Morphologies in the Interpretation of the Electrocardiogram: The Theoretical Basis of the Unipolar Morphologies and Its Correlation with Vectorial Analysis, with Cardiac Activation, and with the Potential Variations at the Epicardial Surface of the Heart. Am. Heart J. **57**: 590 (April) 1959.

In the interpretation of electrocardiograms 2 different basic methods may be employed, namely the vectorial analysis or the study of the morphologies in unipolar leads. The authors point out some of the unanswered questions and limitations of the vectorial method and discuss the physical basis required to interpret the unipolar morphologies as corresponding to the variations in potential in various portions of the heart. Several examples of the utility of the latter method of electrocardiographic analysis are presented. It is concluded that this form of electrocardiographic interpretation gives a wider range of diagnoses than has been obtained so far through vectorial analysis.

SAGALL

Swartwout, J. R., and Walter, E. P.: A Method of Fetal Electrocardiography. Am. J. Obst. & Gynec. **77**: 1100 (May), 1959.

Equipment and technic for fetal electrocardiography are described in detail. A survey of the results in 95 cases of normal pregnancy is reported. A few positive tests were noted between the tenth and fourteenth week of gestation. From the fourteenth week to the thirtieth week of gestation there were between 60 and 80 per cent positive tests. From the thirtieth to the thirty-fourth week there were 90 per cent positive and subsequently there were 100 per cent positive tests. These results relate to the first attempt to obtain a fetal electrocardiogram. The clinical value of fetal electrocardiography lies in its ability to establish the presence of a live fetus. There were no false-positive tests. The factors tending to cause a false-negative test are described.

SHEPS

Van Bogaert, A., Van Genabeek, A., Vandael, J., Arnoldy, M., and Van der Henst, H.: Contribution to the Study of the Q Wave in Peripheral Leads (Experimental Study). Arch. mal. coeur **52**: 241 (Mar.), 1959.

In the dog, secondary or positional Q waves can be made to appear in leads I and aV_L by facilitating contact between the right ventricular surface and the right shoulder, in leads II-III and aV_F by facilitating contact between the left posterior ventricular surface and the dia-

phragm or lower spine. Such Q waves may exceed the R wave in amplitude and duration. Primary Q waves appear in leads II-III in horizontal hearts after crushing of the conduction system in the right ventricle or in the posterior wall of the left ventricle. Conduction delay of the apical and anterior wall brought about by this means causes the Q wave to appear in surface leads and may cause appearance of the Q wave in lead I but not in II and III. Transmural necrosis of the left ventricular wall caused by injection of carbolic acid caused the Q wave to appear in leads II-III in horizontal heart position in posterior as well as anterior location of necrosis, but the Q wave in lead I did not appear in any of 33 animals either in horizontal or vertical heart position. The much higher incidence of Q waves in human infarction may be due to more extensive involvement of the conduction system in this case.

LEPESCHKIN

Zarday, I., Kistof, G., and Solti, F.: The Real Nature of the Extrinsic and Intrinsic Deflections of the Precordial Electrocardiogram. Acta Cardiol. **14**: 158, 1959.

In the authors' opinion, the doctrine of the "extrinsic" and "intrinsic" deflections of the epicardial or precordial electrocardiogram is erroneous, for the "intrinsic" deflection is nothing but the expression of the instantaneous vector of the R deflection in peripheral leads, just as the 2 "extrinsic" deflections are the expressions of the Q and S vectors. Precordial electrocardiography thus does not allow any topographical diagnosis nor any temporal determination of electrical events in the heart. The authors' believe that the theoretical bases of precordial electrocardiography can no longer be sustained. This was corroborated by the fact that in many patients and in animal experiments, clinical or experimental data disagreed with the precordial tracings. Unilateral preponderance of 1 ventricle, changes in the position of the heart, and myocardial injuries can more easily and rationally be diagnosed by the method of "axonometry." A few examples are given.

BRACHFELD

ENDOCARDITIS, MYOCARDITIS, AND PERICARDITIS

Hall, R., and Owen, S. G.: The Hypotensive Effect of Chlorothiazide. Lancet **1**: 129 (Jan. 17), 1959.

The antihypertensive effect of chlorothiazide was studied in 13 patients with hypertension. After a control period, therapy was alternated between a placebo or chlorothiazide. Although no difference was noted between the control or placebo values of blood pressure, a small but statistically significant reduction of blood pressure resulted from 0.5 Gm. chlorothiazide twice daily for 2 months.

KURLAND

Herrman, G.R., Vogelpohl, E. B., Hejtmancic, M. R., and Wright, J. C.: Therapy of Hypertension with Orally Given Syrosingopine. J.A.M.A. **169**: 1609 (April 4), 1959.

Seventy-seven ambulatory patients with essential hypertension were treated orally by syrosingopine. They were separated into 3 groups. In 1 group were 38 patients not previously treated for hypertension. In the second group were 34 patients who had been maintained on therapy with reserpine. In the third group were 5 patients who had been on combination drug therapy and who had severe mental depression or other symptoms of intolerance when maintained on therapy with other antihypertensive drugs. In Group 1, 42 per cent responded with a significant fall in mean blood pressure. In Group II, blood pressure was controlled without side-effects by individual adjustment of dosage. In Group III it was possible (by using 3 mg. syrosingopine per day) to maintain the desired antihypertensive effect without nightmares, nasocongestion, or other side-effects. This absence of severe side-effects is the chief advantage of syrosingopine over other rauwolfia preparations.

KITCHELL

Shucksmith, H. S., and Wilson, G.: Aortic Thrombosis Causing Hypertension. Lancet **1**: 75 (Jan. 10), 1959.

Hypertension is a relatively infrequent complication of thrombosis of the aortic bifurcation. The authors report the case of a 52-year-old woman with intermittent claudication of 8 years' duration and increasing severity. Translumbar aortography showed a block below the renal arteries. A palliative lumbar sympathectomy was performed, but the patient developed severe headaches from newly developed severe hypertension. Accordingly, a thromboendarterectomy of the aorta was performed between the renal arteries, and an aortic bifurcation homograft was inserted communicating with the 2 common femoral arteries. Hypertension and intermittent claudication disappeared.

KURLAND

HYPERTENSION

Haynes, F. W., and Dexter, L.: Pressor Effect of Subcutaneous Renin in Dogs, and Effect of Reserpine, 1-Hydrazinophthalazine and Hexamethonium on Renin Hypertension. Am. J. Physiol. **196**: 502 (Mar.). 1959.

The pressor effect of series of subcutaneous injections of hog renin was studied in the dog, as well as the modifications of the pressor effects of renin by reserpine, hydralazine (1-hydrazinophthalazine), and hexamethonium. In 22 of 27 experiments, short series of subcutaneous renin injections (1 to 37 days) were repeatedly followed by moderate elevations of systolic and diastolic blood pressure. The pressor effect was still noted during oral administrations of reserpine (0.25 mg./day) and hexamethonium (250 to 500 mg./day) but was often absent during the administration of hydralazine (25 mg./day). The pressor response to intravenous renin was increased in animals receiving reserpine and hexamethonium and decreased after hydralazine.

KAYDEN

Horwitz, B., Kuskin, S., and Wang, S. C.: Mechanism of Hypotensive Action of Reserpine. Arch. int. pharmacodyn. **120**: 228, (June), 1959.

The effects of reserpine on the central vasomotor mechanisms were studied in the vagotomized cats under pentobarbital or Dial anesthesia. With the aid of the stereotaxic technic the medullary and hypothalamic vasomotor areas were stimulated. It was found that pressor responses from electric stimulation of these areas were reduced. In addition, the depressor reactions were also reduced by the administration of reserpine. In both anesthetized and decerebrate cats, reserpine was found to lower the blood pressure and to decrease the pressor response following occlusion of the carotid artery. However, these vasomotor events were not closely and quantitatively correlated. These findings indicate that reserpine exerts a general depressive effect on the central vasomotor mechanisms; the suggestion that the drug action is an indirect one, that is, to excite an inhibitory mechanism, is not substantiated.

BRACHFELD

Leishman, A. W. D.: Hypertension—Treated and Untreated. Brit. M. J. **1**: 1361 (May 30), 1959.

The progress of 211 untreated hypertensive patients regularly followed since 1946 was compared with that of 73 patients treated by lumbodorsal sympathectomy and 118 patients treated with ganglion-blocking drugs. The data revealed that treatment significantly lowered the mortality. In particular, the number of patients who died from fatal cerebral hemorrhage was lowered; there were 37 deaths from stroke among 124 untreated patients and only 13 deaths from this cause among 191 patients treated by surgery or ganglion-blocking drugs. In the same group the uremic deaths were 25 in the untreated and 11 in the treated group. It is suggested that ganglion-blocking drugs be used in any man whose diastolic blood pressure is consistently above 120 mm. Hg and, in the presence of albuminuria, treatment is advisable when the blood pressure is below this level. In general, the hypertensive woman does not normally require this intensive treatment unless the diastolic pressure is at least 130 mm. Hg.

KRAUSE

Mathisen, H. S., Jensen, D., Löken, E., and Löken, H.: The Prognosis in Essential Hypertension. Am. Heart J. **57**: 371 (Mar.), 1959.

In 1944 a group of 290 patients (179 women and 11 men) with hypertension were registered from several departments of internal medicine in Oslo. The systolic pressures were 160 mm. Hg or more and the diastolic pressures 95 mm. Hg or more. Their ages were 46 or less. This group was reexamined on several occasions, the last time in 1957. During the observation period none of the patients received special antihypertensive treatment. The prognosis was found to be much better in those patients whose diastolic hypertension was labile (a fall below 95 mm. Hg with bed rest or sedatives) rather than stable. The death rate in patients with labile diastolic hypertension was approximately the same as for the general population in Norway, whereas it was about 5 times higher in the groups with more stabilized diastolic hypertension. The causes of death were cerebrovascular in 55 per cent, cardiac in 24 per cent, and renal in 12 per cent with miscellaneous causes accounting for the remaining 9 per cent.

SAGALL

Newman, M. J. D., and Robertson, J. I. S.: Some Aspects of Prognosis in Treated Hypertension. Brit. M. J. **1**: 1368 (May 30), 1959.

Prognosis in hypertensive patients is influenced by many factors apart from the height of the blood pressure. One hundred and four patients with initial diastolic pressure over 120 mm. Hg were surveyed while under treatment, usually with ganglion-blocking drugs. In the patients with neuroretinopathy, effective lowering of the blood pressure was of great importance in decreasing mortality and morbidity. In the patients with cerebral or cardiac vascular lesions, no such relationship could be discerned. Uncomplicated hyper-

tension (no demonstrable renal, cardiac, retinal, or cerebral involvement) had a relatively good prognosis. The comparative immunity of the female to hypertension was demonstrated, and the authors suggest that, if ganglion-blocking drugs are used in "symptomless" hypertension, probably they should be restricted to young males.

KRAUSE

Rawls, W. B., and Evans, W. L., Jr.: Clinical Experience with Deserpidine in Management of Hypertension and Anxiety Neurosis. New York State J. Med. **59**: 1774 (May 1), 1959.

Deserpidine is an alkaloid derived from *Rauwolfia serpentina*. Forty patients were treated, and 30 of these had hypertension, 19 had symptoms of anxiety neuroses, and 11 were without such symptoms. The average dosage of deserpidine was 0.1 mg. 3 times daily for 5 months. All of the 30 hypertensive patients experienced a reduction in blood pressure, the average fall being 33 mm. Hg in systolic and 14 mm. Hg in diastolic. Eleven of the 29 patients with symptoms of anxiety neurosis experienced complete relief of symptoms and 10 obtained partial relief. Deserpidine apparently induces a satisfactory reduction in anxiety, psychic reactivity, and arterial hypertension with a very low incidence of undesirable side effects often seen with other alkaloids.

KRAUSE

Rice, H. V., and Posener, L. J.: A Practical Method for the Measurement of Systolic Blood Pressures of Infants. Pediatrics **23**: 854 (May), 1959.

The elevated pressure in an arterial occlusion cuff that had been placed proximal to a slightly inflated recording cuff was gradually reduced until visible systolic pulsations occurred on an optical pulse indicator; the pressure in the occluding cuff at the moment that systolic pulsations became visible was taken to be the systolic blood pressure. The new method compared favorably with the auscultatory method but revealed consistently higher values than were obtained in the same subjects by the palpatory and flush technics. The authors concluded that this discrepancy occurred because the latter values were low, whereas the new method provided a more accurate indication of the true systolic level.

KARPMAN

Slater, R. J. Geiger, D. W., Leeson, J., and Gornall, A. G.: Aldosteronism and Hypertension: The Influence of Complete Adrenalectomy upon Essential Hypertension in a Child. Pediatrics **23**: 1125 (June), 1959.

A detailed case report of a 4-year-old boy suffering from intractable, severe, essential hypertension is presented. The maintenance of the hypertension was linked to adrenal function by the increased rate of excretion of aldosterone, the fall in blood pressure during marked dietary restriction of salt, the transient fall in rate of excretion of aldosterone and blood pressure after unilateral adrenalectomy, the absence of excretion of aldosterone and the decrease in blood pressure after total adrenalectomy, and the blood pressure increase in response to salt-retaining hormone. Only a moderate decrease in blood pressure was achieved prior to surgery with rigid salt restriction and administration of hypotensive agents; postoperatively, there was marked improvement in the cardiovascular status concomitant with the decrease in blood pressure.

KARPMAN

Thomas, C. B., and Murphy, E. A.: Observations on Some Possible Precursors of Essential Hypertension and Coronary Artery Disease. VI. Comparison of the Circulatory Reactivity to the Cold Pressor Test and to the Smoking Test. Ann. Int. Med. **50**: 970 (April), 1959.

The ballistocardiographic smoking test and the cold pressor test have been used as standardized stress tests to measure circulatory reactivity. The results of these tests in 386 medical students free from clinical evidence of hypertension or coronary disease are presented. Mean changes in systolic and diastolic blood pressure were plus 13 mm. and plus 16.5 mm. Hg respectively after the cold pressor test. The effects of smoking 1 cigarette upon systolic and diastolic blood pressure were again similar though of smaller magnitude than with the cold pressor test. The effect of age on the response to the smoking and cold pressor tests showed little effect upon the magnitude of the response. This was also true of smoking habits. In general, it could be shown that the circulatory responses to the 2 stimuli of smoking and cold were largely independent of each other. Although some correlation between the 2 tests did seem to exist, it was suggested that both tests be performed in measurement of an individual's circulatory reactivity.

KAYDEN

Winsor, T.: Comparative Effects of Various Rauwolfia Alkaloids in Hypertension. Dis. Chest **34**: 415 (April), 1959.

Eighty patients with benign essential hypertension were studied in 4 groups. Where more than 1 agent was used, the first agent was continued for 1 month after the blood pressure had

come stabilized, discontinued for a month, following which the second agent was instituted. Group I consisted of 20 patients who received a placebo only. The average fall in pressure was mm. Hg systolic, 4 mm. Hg diastolic. The second group received reserpine in an average dose 0.5 mg. daily, which produced an average fall blood pressure of 23 mm. Hg systolic and mm. Hg diastolic. The same group subsequently received the alseroxylon fraction of Rauwolfia, with an average fall in blood pressure of 26 mm. Hg systolic and 12 mm. Hg diastolic. Group III also received reserpine as the initial drug, with an average blood pressure fall of 20 mm. Hg systolic, 15 mm. Hg diastolic. The second drug in this group was rescinnamine given in an average dose of 1.5 mg. daily, which produced an average fall of 8 mm. Hg systolic and 6 mm. Hg diastolic. Group IV received reserpine, but in an average dose of 0.25 mg. daily initially, which resulted in an average fall of blood pressure of 19 mm. Hg systolic, 11 mm. Hg diastolic. The second agent in this group was deserpidine in an average dose of 0.25 mg., which produced a blood pressure fall of 18 mm. Hg systolic and 9 mm. Hg diastolic. Reserpine and the alseroxylon fraction had side effects that were similar in type and magnitude, the predominant one being lethargy. Deserpidine showed lower incidence of side effects as compared with reserpine and alseroxylon. Rescinnamine had an exceedingly low incidence of all side effects, despite the large average dose given.

MAXWELL

Wolfgarten, M., and Magarey, F. R.: Vascular Fibrinoid Necrosis in Hypertension. J. Path. & Bact. **77**: 597 (Apr.), 1959.

Multiple, forceful, centrally directed saline injections were made into the carotid artery of rats and it was observed that peaks of systolic blood pressure up to 330 mm. Hg were obtained. Fibrinoid necrosis was found in 65 per cent of the animals as early as 12 hours after the injections. The necrosis was present in the media of large and small arteries in the kidneys, pancreas, mesentery, and the renal glomeruli, whereas no changes were found in the vessels of the heart or liver. Lesions were found in the large arteries of the animals pretreated with norepinephrine; this effect was thought to be secondary to constriction of the small vessels by the drug. There was a highly significant positive correlation between the maximum peak of the blood pressure obtained and the development of the histologic changes. The authors concluded that these findings support the contention that hypertension per se may lead to fibrinoid necrosis.

KARPMAN

METABOLIC EFFECTS ON CIRCULATION

Villa, L., Dioguardi, N., Agostini, A., Secchi, G. C., Contro, L., Fiorelli, G., Valagussa, L., and Pozza, G.: Behavior of Certain Myocardial Enzymes of the Rat during Acute K-Strophantoside Poisoning. Acta Cardiol. **14**: 135, 1959.

The acute intoxication by K-strophantoside produces in the myocardium of the rat an increase of phosphorylase activity with decrease of active phosphate carriers and with a rise of inorganic phosphorus in distinctly significant quantities; an aldolase increase without increase in lactic acid; a not always significant increase of oxidation in the Krebs cycle; a modification in the enzymatic systems of protein and lipid metabolism which remain to be evaluated; and a large increase in serum potassium. The changes in phosphates were, in the authors' opinion, the most important. They believed that there may be a correlation between these findings and the changes in aldolase levels and in the Krebs cycle in the direction of active phosphate system activation produced by the intoxication, without corresponding increase in oxidative activity. Since the intoxication is reversible the authors' think that this disequilibrium is being compensated in a slower, after phase. Other aspects of the toxic state necessitate further investigations.

BRACHFELD

PATHOLOGY

Lumb, G., Schacklett, R. S., and Dawkins, W. A.: The Cardiac Conduction Tissue and Its Blood Supply in the Dog. Am. J. Path. **35**: 467 (May-June), 1959.

Arterial branches supplying the atrioventricular node and bundle of His were selectively ligated in mongrel dogs and the resultant distribution of infarction was carefully studied. The high mortality resulting from occlusion of the anterior and posterior septal arteries indicated that there was no other significant blood supply to the conduction system. Evidence was accumulated which indicated that injury to conduction tissue fibers in the upper intraventricular septum was responsible for making ischemia of that region such a lethal condition.

KARPMAN

Selye, H., and Bajusz, E.: Sensitization by Potassium Deficiency for the Production of Myocardial Necrosis by Stress. Am. J. Path. **35**: 525 (May-June), 1959.

No structural alterations in the myocardium were noted in rats maintained for 1 week on a diet deficient in potassium and magnesium. Extensive

myocardial necrosis was then produced in these animals by a variety of stressful stimuli (norepinephrine, vasopressin, thyroxine, dihydrotachysterol, plasmocid, forced restraint, cold or hot baths, vagotomy, quadriplegia, and intestinal trauma), whereas these stimuli were ineffective in producing this lesion in animals on a normal diet. The authors conclude that a brief period of nutritional deficiency can selectively condition the myocardium to the cardiotoxic effects of various forms of stress.

KARPMAN

Wasserman, F., Brodsky, L., Kathe, J. H., Dick, M. M., and Rodensky, P. L.: Treatment of Procaine Amide Intoxication. An Experimental Study. Am. J. Cardiol. 3: 758 (June), 1959.

Procaine amide solution was infused into 20 dogs until there was advanced cardiotoxicity as indicated by QRS widening up to 0.20 second; premature atrial, nodal or ventricular beats; atrioventricular dissociation; atrial fibrillation; or nodal or ventricular tachycardia. Hypotension was a late toxic feature. Because of the efficacy of molar sodium lactate in accelerating intraventricular conduction delayed by other causes, amounts up to 80 mEq. were promptly infused into 10 dogs, and striking electrocardiographic improvement was noted in each instance. That the improvement was not due simply to a wearing off of procaine effect was evidenced by the 5-fold slower rate of QRS recovery in animals not given sodium lactate. A prior dose of 30 to 45 mEq. of molar lactate in 3 animals appeared markedly to increase the tolerance to procaine amide. In 1 experiment, an arrhythmia previously considered to be an irreversible manifestation of procaine intoxication—slow idioventricular rhythm—failed to respond well to sodium lactate, then promptly reverted to sinus rhythm when norepinephrine was added to the lactate therapy. The authors are impressed that the combination of molar sodium lactate plus norepinephrine may be the treatment of choice in severe procaine amide intoxication.

ROGERS

PHARMACOLOGY

Daly, M. D., and Luck, C. P.: The Effects of Adrenaline and Noradrenaline on Pulmonary Haemodynamics with Special Reference to the Role of Reflexes from Carotid Sinus Baroreceptors. J. Physiol. 145: 108 (Jan. 28), 1959.

A rotometer was used to measure pulmonary blood flow in artificially ventilated anesthetized dogs. Epinephrine and norepinephrine administered intravenously produced a bradycardia and a slight elevation in systemic blood pressure; the pulmonary arterial pressure and blood flow decreased initially and then increased above control values as the heart rate gradually returned to its original level. The results of experiments utilizing atropine, division of the cervical vagosympathetic nerves, or exclusion of the carotid sinuses from the circulation suggested that the rise in systemic blood pressure reflexly produced the bradycardia and the initial transient effects of pulmonary artery pressure and flow by stimulation of the baroreceptors in the carotid sinuses. The reflex compensatory adjustments in pulmonary blood flow were thought to be due to the bradycardia and to an effect on the peripheral blood vessels which were opposite to the vasoconstrictive action of the amine.

KARPMAN

Duff, R. S.: Peripheral Effects of "Vasculit." Brit. M. J. 1: 1007 (April 18), 1959.

Vasculit is the butyl derivative of the para-oxy homologue of phenylephrine. The effects of infusing it into the brachial artery were measured with plethysmographs in a group of hospitalized patients under controlled conditions. Vasculit in the average dose of 0.6 mg. caused an increase in blood flow, in the infused hand, averaging 57 per cent. The dilator effect was in the periphery and was sufficient to counteract the constrictor effect of simultaneously infused epinephrine. In general, no systemic effects from the drug were apparent; the effect of vasculit did not appear to depend on the initial level of blood flow and it lasted for only the duration of the infusion.

KRAUSE

Flacke, W.: Studies on Veratrum Alkaloids. XXVIII. The Action of the Erythrophleum Alkaloids on the Single Twitch and on the "Veratrine Response" of the Sartorius Muscle of the Frog. J. Pharmacol. & Exper. Therap. 125: 49 (Jan.), 1959.

The antiveratrinic activity of a series of erythrophleum alkaloids was examined in the isolated sartorius muscle of the frog. All alkaloids studied were active. These included cassaine hydrochloride, cassaidine hydrochloride, erythrophleine sulfate, coumingine hydrochloride and acetyleassaidine hydrochloride. Of the breakdown products cassainic acid and cassaidinic acid; methylaminoethanol and dimethylaminoethanol were examined. In addition, a synthetic ester, dimethylaminoethanol pimelate, was used. As with the cardiac glycosides the potency of the alkaloids in antagonizing the effect of a given concentration of veratridine in skeletal muscle

paralleled closely their positive inotropic potency in the vertebrate heart. This parallelism extended also to a synthetic ester, dimethylaminoethanol melate, which differs from the native alkaloids only in the acid involved, and to the breakdown products. The type of antiveratrinic activity of these alkaloids is similar to that of the cardiac glycosides. In both cases pretreatment did not prevent the appearance of a transient veratrine response. The development of the antiveratrinic effect depended upon activity of the muscle. The duration of the pretreatment did not influence the time course of the antiveratrinic action. This typical time course was therefore independent of a process of diffusion of the alkaloids to the site of action.

RINZLER

Foster, J. H., and Killen, D. A.: Aortography and Arteriography: An Analysis of Results in a University Medical School. Ann. Surg. **19:** 321 (Mar.), 1959.

A critical and comprehensive survey of the available material at Vanderbilt University Hospital and Thayer Veteran's Administration Hospital was carried out. Each arteriogram was analyzed as regards anesthesia, dye employed, injection technic, radiologic technic, interpretation of films, post arteriogram course and subsequent operative findings. Of 25 thoracic aortograms, 18 yielded diagnostic results. Among 127 abdominal aortograms, 89 yielded diagnostic results. Among 81 in the peripheral arteriograms there were 61 per cent diagnostic results. These procedures all entail definite risk and should be undertaken only with good indication. There are several points which stand out in the ability to obtain diagnostic films with the least complications. Single injections of the dye, meticulous insertion of the needle, local anesthesia when possible, rapid serial exposures of x-ray films or prolonged exposure, use of dye with minimal toxicity and more careful patient selection are the most important factors in success. Prolonged single exposure of the x-ray film seems particularly valuable in peripheral arteriography. The least toxic dye currently is a 50-90 per cent solution of Hypaque. In this series there were 4 instances of major complications, 2 following percutaneous femoral arteriograms and 2 following transiumbar aortograms. In the former, amputation was necessary because of popliteal thrombosis. In the latter, death occurred 5 days after the procedure in 1 patient and a persistent paraplegia in the other. Some of the lesser complications included skin rashes, Horner's syndrome, transient ischemia of arm, gross hematuria, severe back pain, nausea and vomiting, and transient hypotension. In thoracic aortography a rapid injection of dye is crucial. The total amount of dye needed varies. Allergic reactions are best avoided by first testing the patient with an injection of a small amount of the dye. General anesthesia seems to predispose to serious complications. Bleeding tendencies, renal disease, severe cardiopulmonary disease, age, arteriosclerotic occlusion of terminal aorta, hypertension, allergy and aneurysm of the aorta predispose to complications. The authors point out that in the overall series there has been a failure in 32 per cent of patients to obtain diagnostic films. This appears excessive to the authors and they recommend that future reports on these procedures include evidence of success and failure.

LEVINSON

Gold, H., and Corday, E.: Vasopressor Therapy in Cardiac Arrhythmias. New England J. Med. **206:** 1151 (June 4), 1959.

Six cases are presented as examples of cardiac arrhythmias which may be terminated when the systemic blood pressure is raised to normal levels by intravenously administered vasopressor drugs. The abnormal rhythms so converted included premature systoles, atrial and ventricular tachycardias, atrial fibrillation, sinus bradycardia, and heart block when they were associated with hypotension. In patients with severe coronary artery disease hypotension resulting from tachycardia should be treated with vasopressor agents as soon as vagal-stimulating measures fail to stop the arrhythmia. In such situations vasopressor drugs, even if they fail to convert the abnormal rhythm, still are indicated because they sustain the coronary blood flow until other antiarrhythmic agents act. Short-acting vasopressor agents whose action may be abruptly terminated if necessary should be employed exclusively because raising of the blood pressure to excessive levels may induce serious ventricular arrhythmias. Vasopressor drugs have been found to be safe in the treatment of abnormal cardiac rhythms and may prevent serious myocardial damage or death when acute coronary occlusion precipitates an arrhythmia.

SAGALL

Hanna, C.: Papaverine Analogs. VII. Studies on the Time of Onset of Coronary Dilator Action. Arch. int. Pharmacodyn. **119:** 162 (Mar.), 1959.

The time of onset of the coronary vasodilator action of papaverine and related analogs has

been studied by the Langendorff rabbit heart preparation. It was found that the time of onset and the length of coronary dilator action were related to the size and type of ether groups on the isoquinoline nucleus of the papaverine analogs. These results were confirmed by means of 2 new papaverine analogs, 1 of which exhibited a greater coronary vasodilator potency than either papaverine or ethaverine.

BRACHFELD

Mercier, F., Mercier, J., Gavend, M., and Gavend, M. R.: Study of Certain Dynamic and Energetic Aspects of the Cardiac Action of Digitalis Glucosides and Sparteine. Arch. mal. coeur **52**: 177 (Feb.), 1959.

In dogs, the heart output was measured by the principle of Fick, and cardiac work was calculated from the output and the arterial pressure; coronary flow was measured by cannulation of the coronary sinus while the myocardial oxygen consumption was calculated from this and the coronary arteriovenous oxygen difference. Digitalin, Ouabain, Digoxin, and adonidoside in clinical doses caused a greater decrease of cardiac work than of myocardial oxygen consumption, resulting in a decrease of cardiac work efficiency, especially at high concentrations. On the contrary, sparteine (5 to 10 mg./Kg.) caused a greater reduction of myocardial oxygen consumption than of cardiac output, resulting in an increased cardiac work efficiency.

LEPESCHKIN

Nordqvist, P., Cramer, G., and Bjorntorp, P.: Thrombocytopenia during Chlorothiazide Treatment. Lancet **1**: 268 (Feb.), 1959.

Thrombocytopenia developed during chlorothiazide therapy in 6 patients. In 2 patients, the evidence was direct; in a third, in vitro tests for chlorothiazide effect was positive. The other 3 were less definite. Three of the 6 also had a purpuric rash. In all patients, the thrombocytopenia was the only toxic manifestation in the bone narrow. The reaction was usually brief, and platelet count returned to normal as soon as chlorothiazide was withdrawn.

KURLAND

Pepeu, G., Masi, R., and Giotti, A.: Nicotine-like Actions of Ephedrine on Isolated Guinea Pig Auricles. Arch. int. pharmacodyn. **119**: 334 (Apr.), 1959.

The stimulating action of small doses of ephedrine (10^{-6}, 10^{-5}) on isolated guinea pig atria was suppressed by nicotine (5×10^{-5}), hexamethonium (4×10^{-4}) and atropine (10^{-5}), whereas the depressing action of higher doses (10^{-4}) was not suppressed by these substances but rather unmasked. Small doses of ephedrine (10^{-6}, 5×10^{-6}) reduced or abolished the cholinergic effect of nicotine and higher doses (5×10^{-5}, 10^{-4}) also impeded the sympathergic effect of nicotine. Whether small or high, doses of ephedrine did not impede the muscarinic action of acetylcholine, and they retarded, but did not prevent, the positive inotropic and chronotropic action of epinephrine. The stimulating action of ephedrine showed tachyphylaxis, but its antinicotinic action did not. Ephedrine, in its action on guinea pig atria, may be considered a nicotine-like drug.

BRACHFELD

Plummer, A. J., Barrett, W. E., Maxwell, R. A., Finocchio, D., Lucas, R. A., and Earl, A. E.: Hypotensive Properties of Syrosingopine, SU-3118, an Ester of Methyl Reserpate. Arch. int. Pharmacodyn. **119**: 245 (Mar.), 1959.

Syrosingopine, Su-3118, closely resembles reserpine in chemical structure and its capacity to cause hypotension and bradycardia in the unanesthetized normotensive and neurogenic hypertensive dog as well as in the cat under Dial anesthesia. There was some divergence, however, in the central sedative properties of these substances. For example, a dose of syrosingopine 40 times that of reserpine was required to eliminate the behavioral expression of fear and anxiety in conditioned rats subjected to a stressful situation, and 20 times more syrosingopine than reserpine was required to cause an equivalent decrease in the spontaneous activity of mice. Since the sedating influence of syrosingopine was much less prominent than that of reserpine in the dog, mouse, and rat, the cardiovascular actions of the former could be achieved without evoking the quieting effect characteristic of the latter.

BRACHFELD

Szekeres, L., Lenard, G., and Torok, T.: Effect of Strophanthine on Myocardial Metabolism of Normal and Hypoxic Rats. Arch. int. Pharmacodyn. **119**: 102 (Mar.), 1959.

The action of strophanthin on oxygen uptake, anaerobic glycolysis, and on high energy phosphate and glycogen content of normal and hypoxic rat myocardium was studied. Strophanthin, 10^{-4} M and 10^{-6} M, significantly increased oxygen cosumption of slices of normal rat heart. In heart muscle slices of hypoxic animals strophanthin failed to increase tissue respiration.

Strophanthin reduced anaerobic glycolysis both in normal and in hypoxic hearts. Strophanthin could not prevent the decrease in high energy phosphates and glycogen contents of the heart induced by hypoxia.

BRACHFELD

Thorp, R. H.: The Effect of Ouabain on the Heart Block Produced in the Guinea Pig by 2-Chloroadenosine. Arch. int. pharmacodyn. **120**: 129 (June), 1959.

The influence of ouabain on heart block produced by intraatrial injections of 2-chloroadenosine in the guinea pig was examined. Heart block was produced by 2-chloroadenosine with doses of 1 to 5 μg., whereas with adenosine a dose of 10 to 50 μg. was required. The block produced by 2-chloroadenosine was always more prolonged than that produced by adenosine, since it was not subject to destruction by adenosine deaminase. Ouabain had no significant effect upon the duration of the heart block produced by 2-chloroadenosine. 2-Chloroadenosine has no cardiotonic effect upon the isolate hypodynamic papillary muscle of the cat. These results are discussed in relation to the potentiation of the adenosine heart block by cardiac glycosides.

BRACHFELD

Von Capeller, D., Copeland, G. D., and Stern, T. N.: Digitalis Intoxication: A Clinical Report of 148 Cases. Ann. Int. Med. **50**: 869 (April), 1959.

The authors have reviewed the clinical records and electrocardiograms of patients with digitalis intoxication. The criterion used for establishing this diagnosis was that the symptoms or the electrocardiographic signs of digitalis intoxication disappear upon discontinuing digitalis medication. The diagnosis was made more frequently in recent years and the majority of patients were those in severe congestive heart failure. The initial clinical manifestations of digitalis intoxication were most often anorexia, nausea, and cardiac irregularities. The next most common sign of intoxication was an increase in severity of congestive heart failure, which improved when the digitalis was omitted. One quarter of the series had electrocardiographic changes as the sole evidence of digitalis intoxication, but the great majority of patients had both signs and symptoms of intoxication. The types of arrhythmias and conduction defects were analyzed. Multifocal premature ventricular systoles were the most common electrocardiographic abnormality (58 per cent) and one third of the patients had bigeminal rhythm. Digitalis leaf was the most frequent preparation responsible for intoxication (66 per cent) and a maintenance dose of .083 Gm. frequently produced intoxication. Digitalis intoxication was thought to be the cause of death in 6 patients.

KAYDEN

PHYSICAL SIGNS

Cassels, D. E.: Use of the Stethoscope in Pediatric Cardiology. J.A.M.A. **170**: 781 (June 13), 1959.

The stethoscope remains the major instrument in pediatric cardiology. It is portable, informative, and adaptable in many situations, and its use is not limited to the chest. Hemodynamic sounds can be followed either to their point of maximum intensity or to their disappearance. In children the pliability of the thoracic wall makes auscultation especially informative because heart sounds may change during manipulation of the chest. This facilitates investigation of both functional and organic murmurs. At least 4 characteristic murmurs or cardiovascular noises not related to disease occur in children up to 12 and 15 years of age and are described. The stethoscope is the only instrument permitting bedside investigation of these interesting and significant phenomena.

KITCHELL

Morton, W., Beaver, M. E. N., and Arnold, R. C.: Heart Disease Screening in Elementary School Children. J.A.M.A. **169**: 1163 (Mar. 14), 1959.

A screening program for congenital and rheumatic heart disease was carried out among 6,311 children between the ages of 6 and 11 years. One hundred and sixty-five were identified as requiring further study, and a second program of examinations was carried out. Abnormalities discovered included 33 cases of congenital and 7 of rheumatic heart disease. The study revealed 29 cases of previously unrecognized cardiac abnormality but also relieved at least 15 children of a false diagnosis of heart disease. It was interesting to note that of the children without heart disease 33 per cent had innocent heart murmurs.

KITCHELL

Morton, W., Hoffman, M. S., and Dodge, H. J.: Comparison of Three Methods of Screening for Pediatric Heart Disease. J.A.M.A. **169**: 1169 (Mar. 14), 1959.

Three screening methods were compared as to specificity and sensitiveness in detecting cardiac abnormalities in examination of 5,654 children. The 3 methods consisted of a single lead V_{3R} electrocardiogram, miniature chest roentgenogram, and

limited physical examination. The V_{3R} lead was fairly sensitive in the detection of right ventricular hypertrophy. Of 58 children with abnormal V_{3R} tracings, 11 had right ventricular hypertrophy, 3 had electrocardiographic abnormalities, and 44 had normal hearts. Thus, the electrocardiogram was an ancillary and not a primary diagnostic tool. The chest x-ray was not a sensitive tool in the detection of heart disease in children. Physical examination used singly was the most specific and most sensitive and gave the highest efficiency index. It was emphasized that none of these methods of screening is infallible.

KITCHELL

PHYSIOLOGY

Bauereisen, E., Böhme, H., Krug, H. Peiper, U., and Schlicher, L.: Reliability of Intracardiac Pressure Measurements in Furnishing Information Concerning Adaptation of the Heart in Situ. Ztschr. Kreislaufforsch. 48: 372 (April), 1959.

In dogs, right and left intraventricular pressures and the intraplural pressure were registered synchronously through catheters; diastolic pressures were registered by special channels with high sensitivity. When ventricular filling was increased by intravenous infusion after hemorrhage, a positive correlation was usually found between transmural diastolic filling pressure and systolic pressure amplitude for both ventricles. Increase of ventricular filling during spontaneous inspiration was usually characterized by absent correlation between filling pressure and systolic amplitude in both ventricles; less commonly the correlation was negative in both ventricles or positive in the right and negative in the left ventricle. In the latter case the pulmonary arterial pressure was always abnormally high. In isolated lungs the peripheral arterial resistance decreased considerably with increase of perfusion pressure and especially with distention of the lung; this decrease disappeared in pulmonary edema or at very high perfusion pressures. This observation would explain the negative or absent correlation in the right ventricle during respiration. The negative correlation in the left ventricle could be explained by a reflex systemic vasodilatation during inspiration; however, it could not be made positive by ganglionic-blocking agents. A positive correlation, which corresponds to Starling's law, can therefore be masked by complicating factors acting at the same time on the arterial resistance.

LEPESCHKIN

Benforado, J. M.: The Effects of Vagal Stimulation on the Isolated Perfused Rat Heart. J. Physiol. 145: 266 (Mar. 3), 1959.

Isolated rat hearts were perfused with a phosphate-bicarbonate Ringer's solution in which the vagal nerves remained viable for at least 6 hours. Vagal stimulation produced arrhythmias or varying degrees of heart block; the effects were related to the intensity and duration of stimulation. A comparison of the results of independent right and left vagal stimulation in preparations in which both nerves were viable revealed no differences in the effect on sinoatrial rate, heart block, ectopic beats, extrasystoles, or increases in rate following cessation of stimulation. Physostigmine and ouabain augmented the effects of vagal stimulation, whereas atropine and hexamethonium antagonized them. The author suggested that suppression of higher pacemaker activity was a necessary antecedent to the arrhythmias produced by vagal stimulation in the absence of any predisposing factors.

KARPMAN

Borison, H. L., and Kovacs, B. A.: Central Mechanisms in Pulmonary Oedema of Nervous Origin in Guinea Pigs. J. Physiol. 145: 374 (Mar. 3), 1959.

Criteria based on increased lung weight and gross pathologic changes in the lungs were established for evaluating the development of vagotomy-induced pulmonary edema in the guinea pig. Acute pulmonary edema was produced in animals subjected to bilateral vagotomy or transection of the spinal cord at C7. Decerebrate guinea pigs developed pulmonary edema after bilateral vagotomy but not after section of the cervical cord; if the decerebrate animals were artificially ventilated, bilateral vagotomy did not produce pulmonary edema. Discrete lesions in the vagal nuclei resulted in pulmonary edema in normal and decerebrate animals, whereas asymmetric lesions (which partially spared the vagal nuclei) resulted in delayed pulmonary edema. Since neurogenic pulmonary edema was produced in the absence of neural connections between the central nervous system and the circulatory system, parabiotic experiments were performed upon decerebrate guinea pigs and it was observed that some protection against the edema of vagotomized parabions was obtained by combination with a nonvagotomized partner. The authors suggest that a humoral mechanism may be involved in vagotomy-induced pulmonary edema.

KARPMAN

Coleridge, J. C. G., and Linden, R. J.: The Variations with Respiration in Effective Right and Left Atrial Pressures in the Dog. J. Physiol. 145: 482 (Mar. 12), 1959.

The effects of respiration on the effective right and left atrial pressures were investigated by a closed technic (i.e., without the need of a tho-

cotomy) in the anesthetized dog. Pressure measurements were made just before the onset of atrial systole, at the height of atrial contraction and just before the second heart sound. The latter pressure measurement in the right atrium always increased with normal inspiration and decreased with positive-pressure inflation, whereas in the left atrium it tended to remain steady or fall at the beginning of inspiration, rise to a peak during expiration, and act in variable fashion during positive-pressure inflation. The other 2 pressure measurements followed a similar course during inspiration when the heart rate was regular but they decreased throughout inspiration when the heart rate was rapid. The authors conclude that the atrial receptor discharge may be influenced by numerous factors and that among the most important are active or passive changes in tension of the atrial wall that produce changes in the effective atrial pressures.

KARPMAN

Coles, D. R., and Cooper, K. E.: Hyperaemia following Arterial Occlusion or Exercise in the Warm and Cold Human Forearm. J. Physiol. **145**: 241 (Mar. 3), 1959.

Water-filled venous occlusion plethysmographs were used to measure blood flows in the forearm. Reactive hyperemia, which was induced by a short period of circulatory arrest, was reduced in the forearm as the limb muscle temperature was reduced to 19-25 C. In the warm arm it occurred in both the skin and muscle while, in the cold arm, the vasodilatation occurred primarily in the deeper tissues and not in the skin. Hyperemia after exercise occurred only in the deep tissues and was not influenced significantly by cooling of the forearm. The degree of increase in blood flow following exercise was found to be related to the amount of work performed. The authors suggest that, after its physical properties have been altered by a cold temperature, the muscle undergoing rhythmic contractions has a higher metabolism with a consequent increase in the production of vasodilator metabolites.

KARPMAN

Corday, E., Gold, H., De Vera, L. B., Williams, J. H., and Fields, J.: Effect of the Cardiac Arrhythmias on the Coronary and Systemic Circulations. Ann. Int. Med. **50**: 535 (Mar.), 1959.

Comparative measurements of coronary artery and coronary sinus flow, coronary blood pressure and systemic blood pressure, and cardiac output and venous pressure were made in animals during regular sinus rhythm, premature atrial and ventricular systoles, atrial tachycardia, flutter and fibrillation, and during ventricular tachycardia and fibrillation. Coronary artery flow was usually reduced during these arrhythmias but coronary sinus flow showed marked fluctuation. One possible explanation for the lack of correlation between coronary artery and coronary sinus flow may be the presence of shunts in the myocardium that open in response to ischemia. Systemic artery pressure was also lowered during these arrhythmias and coronary artery flow appeared to decline in a linear fashion as systemic blood pressure fell. The authors believe that the presence of systemic hypotension during atrial or ventricular arrhythmias warrants the use of vasopressor agents to restore the blood pressure. It was observed that vasopressor agents frequently abolished the arrhythmia directly. This effect was thought to be due to a direct action on the heart rather than solely via the vagus nerve. Since most of the tachycardias appeared to reduce coronary flow, it was suggested that patients with these arrhythmias be treated promptly to restore nutritional supply to myocardium.

KAYDEN

Corday, E., Williams, J. H., DeVera, L. B., and Gold, H.: Effect of Blood Pressure and Vasopressor Drugs on Coronary Blood Flow and the Electrocardiogram. Am. J. Cardiol. **3**: 626 (May), 1959.

The rate of blood flow from the proximal and distal ends of the severed anterior descending coronary artery of dogs was measured by an open-drop method, by a Shipley rotameter, or by a photoelectric dropmeter under various experimental conditions. During hypotension coronary flows were regularly diminished and T waves were lowered. These changes were restored by elevating the blood pressure, either by transfusion or by a vasopressor drug. Raising the blood pressure 20 mm. Hg increased the coronary flow approximately 30 per cent. When hypertension above 180 mm. Hg systolic was induced by aortic snare or by a vasopressor drug, ventricular or nodal arrhythmias appeared and terminated when normotension was effected. The clinical application of these experimental observations is discussed.

ROGERS

De Carvalho, A. P., De Mello, W. C., and Hoffman, B. F.: Electrophysiological Evidence for Specialized Fiber Types in Rabbit Atrium. Am. J. Physiol. **196**: 483 (Mar.), 1959.

Intracellular microelectrodes were used to study the site of origin and direction of spread of activity in the rabbit atrium. Pacemaker poten-

tiality was found only in tissues derived from embryologically distinct structures such as the sinus venosus, the venosus valves, and the lower segment of the atrial canal. Activity normally spread slowly from the sinoatrial node and excited the crista terminalis along a broad front. Spread was then rapid through the crista, the pectinate muscles, and the fibers of the atrial roof. The septum was normally excited from the crista terminalis. Excitation reached the atrioventricular node almost simultaneously from the crista terminalis and the right segment of the sinoatrial ring bundle. This latter showed many characteristics of specialized conducting tissue. Around the atrioventricular ring conduction, velocity slowed markedly in fibers that had many of the electrophysiologic characteristics of atrioventricular nodal fibers.

KAYDEN

Delaunois, A. L., Kordecki, R., Polet, and Ryzewski, J.: Cardiac Output, Arterial Blood Pressure and Pulmonary Arterial Pressure in Histamine Shock. Arch. int. pharmacodyn. **120**: 114 (May), 1959.

Histamine, administered intravenously in doses from 250 to 300 μg. per Kg. of body weight, induced a pronounced fall of systemic arterial blood pressure in dogs anesthetized with morphine and chloralose. Parallel to the fall in systemic blood pressure, a slight increase in pulmonary arterial pressure occurred, which persisted during the whole period of lowered systemic arterial pressure. The cardiac output increased 10 seconds after the onset of the fall in systemic blood pressure induced by histamine and returned to its initial level later than the systemic blood pressure. It was concluded that the fall in systemic blood pressure in histamine shock is not due to primary cardiac failure.

BRACHFELD

Donald, K. W.: Exercise and Heart Disease. Brit. M. J. **1**: 985 (April 18), 1959.

The effects of exercise were studied in patients with mitral stenosis, none of whom were in congestive heart failure at the time of the investigation. All subjects were mildly sedated and lay supine. Cardiac catheterization was accomplished and the catheter tip was introduced into the pulmonary artery. Arterial blood samples were obtained from an indwelling needle in the brachial artery. Exercise was performed on a bicycle ergometer attached to the table. A low level of mixed venous blood saturation was frequently encountered during exercise and it was assumed that this could only be accomplished by a considerable reduction of blood flow to the parts of the body not involved in the exercise. For this reason regional blood flow studies were undertaken. It was first determined that the blood flow to the exercising muscles was about 80 per cent of that found in normal subjects with a normal cardiac output response to effort. As the cardiac output was low and fixed, this could only be achieved by a very considerable reduction of blood flow to the whole skin, to muscles not involved in the exercise, to the splanchnic area, and to the kidneys. Only the cerebral blood flow was exempt and continued at the resting level. No patient complained of symptoms suggesting ischemic heart pain during exercise and the author assumed that coronary blood flow was not compromised. Both humoral and neural mechanisms were presumed to be responsible for the integrated circulatory economy demonstrated in cardiac patients under exercise condition.

KRAUSE

Eckstein, J. W., and Hamilton, W. K.: Effects of Isoproterenol on Peripheral Venous Tone and Transmural Right Atrial Pressure in Man. J. Clin. Invest. **38**: 342 (Feb.), 1959.

Emphasizing the fact that the transmural pressure (difference between intra-atrial and intrapleural pressure) is the actual pressure which distends the atrium, the authors have measured right atrial pressure and esophageal pressure (as a measure of intrapleural pressure) plus end-expiratory carbon dioxide concentration before and during an intravenous infusion of isoproterenol (5.8 μg./min) in 5 control subjects. In each case the isoproterenol caused a significant increase in ventilation and a simultaneous decrease in end-expiratory carbon dioxide tension. In spite of this hyperventilation, no consistent change was noted in mean esophageal pressure. Right atrial pressure and transmural right atrial pressure fell significantly, however. In 5 additional subjects forearm venous pressure-volume curves were constructed before, during, and after similar intravenous isoproterenol infusions. In 4 of the 5 subjects the forearm venous pressure fell during the infusion and in all subjects the venous distensibility (venous volume at venous pressure of 30 mm. Hg) fell. The venous volume decreased by an average of 39.5 per cent of which 34.2 per cent could be accounted for by venous constriction while the remaining 5.3 per cent decrease was attributable to the fall in distending pressure. Although hyperventilation also caused venous constriction the authors believe that the results noted were largely due to the isoproterenol infusion. Since transmural atrial

essure fell, while venous constriction caused a ntral shift of blood, the results tended to rein- rce indirectly the thesis that isoproterenol s an effect on the myocardium which causes creased cardiac output.

FREEDBERG

ank, N. R., Radford, E. P., Jr., and Whittenberger, J. L.: Static Volume-Pressure Interrelations of the Lung and Pulmonary Blood Vessels in Excised Cats' Lungs. J. Appl. Physiol. **14:** 167 (Mar.), 1959.

The authors studied the influence exerted by e lungs and pulmonary blood vessels on elastic havior. For this purpose, measurements were ade of the effect of pulmonary vascular dis- ntion on static-volume pressure relations of cised cats' lungs filled either with saline to inimize surface forces, or inflated with gas. The results showed that only slight changes of ques- onable significance occurred in elastic behavior of the lungs during deflation when pulmonary vascular pressure was increased from 0 to 16 cm. of water. The vascular volume-pressure curve was considerably flattened in gas-inflated lungs at airway pressures above 10 cm. of water. During filling and emptying of the vascular system there were slight but definite changes in equilibrium volume of the lung.

RINZLER

Goodford, P. J.: The Loss of Potassium from Isolated Rabbit Atria. J. Physiol. **145:** 221 (Mar. 3), 1959.

The concentration of potassium was determined in 29 pairs of rabbit atria that had been beating in Ringer-Locke solution for different lengths of time. The results indicated that the atria lost potassium as they continued to contract and that the fall was greatest in atria that were allowed to beat until they had ceased spontaneously. The author concluded that the arrest of contractions was related to the alteration in membrane potential due to the fall in internal potassium and that acetylcholine started contraction probably by alter- ing the membrane potential.

KARPMAN

reenspan, R. H., Lester, R. G., Marvin, J. F., and Amplatz, K.: Isotope Circulation Studies in Congenital Heart Disease. J.A.M.A. **169:** 667 (Feb. 14), 1959.

A new procedure has been developed for the tection of shunts. This consists of the injec- n of trace amounts of a radioisotope into the rious cardiac chambers and the vessels. Ap- arance times and concentration slopes are then corded by means of externally placed colli- mated scintillation counters. This method obviates the need for arterial puncture. The method has been used qualitatively but would appear to lend itself well to quantitative studies of circulation dynamics. The apparatus needed has been reduced to a compact portable unit. The method is simple, requires little time, and the use of a quickly excreted radioisotope reduces radiation hazard to a minimum.

KITCHELL

Guyton, A. C., Abernathy, B., Langston, J. B., Kaufmann, B. N., and Fairchild, H. M.: Relative Importance of Venous and Arterial Resistances in Controlling Venous Return and Cardiac Output. Am. J. Physiol. **196:** 1008 (May), 1959.

In dogs with cardiovascular reflexes completely blocked by complete spinal anesthesia, the total peripheral resistance was increased by 2 methods: first, by injecting small plastic microspheres into the arteries, thereby increasing arterial resistance, and, second, by inflating pneumatic cuffs around the major veins, causing increased venous resistance. A comparison of the effects of the increases showed that a small increase in venous resistance decreased cardiac output 8 times as much as an increase in arterial resistance of similar magnitude. This difference was caused principally by a marked rise in systemic arterial pressure when arterial resistance was increased, which thus maintained the cardiac output at almost normal levels. In contrast, a rise in venous resistance caused a fall in systemic arterial pressure, which resulted in an even greater decrease in cardiac output than an increased total peripheral resistance alone would have caused.

KAYDEN

Huckabee, W. E.,: The Role of Anaerobic Metabolism in the Performance of Mild Muscular Work. II. The Effect of Asymptomatic Heart Disease. J. Clin. Invest. **37:** 1593 (Nov.), 1958.

This paper reports on similar studies of 30 patients with heart disease without evidence of heart failure (Class I) in whom it was found that oxygen consumption, cardiac output, arteriovenous oxygen difference, blood pyruvate and blood lactate levels were all within the normal range. The anaerobic metabolic rate was also normal; however, when the "per cent response of cardiac output" (the cardiac output deficit or the amount of additional output which would have been required to supply the extra oxygen so that metabolism would be totally aerobic) was calculated, this was found to be abnormal in all 9 patients with atrio-ventricular valvu-

lar disease. Those with aortic stenosis, arterial hypertension and pulmonic valvular disease did not show this abnormality at a stage when the other determinations were normal and failure had not occurred. Patients with mitral stenosis appear to be unable to increase their cardiac output to meet the demands of mild exercise and they must meet their tissue energy requirements by reliance upon other mechanisms. The author draws a parallel between these results and the well known clinical history of patients with mitral valvular disease who within 5 to 10 years following acute rheumatic fever begin a slow downhill path of symptomatic cardiac insufficiency as compared to those with aortic valvular deformity who seem to have no physiologic difficulty for many years until heart failure occurs, at which time their cardiovascular function rapidly deteriorates.

FREEDBERG

Huckabee, W. E., and Judson, W. E.: The Role of Anaerobic Metabolism in the Performance of Mild Muscular Work. I. Relationship to Oxygen Consumption and Cardiac Output, and the Effect of Congestive Heart Failure. J. Clin. Invest. **37**: 1577 (Nov.), 1958.

The authors extended previous investigations of anaerobic metabolism, by comparing the amount of energy supplied by the anaerobic pathway during mild exercise in a group of normal subjects to that in a group of patients with either valvular or arteriosclerotic heart disease and superimposed congestive failure. By determining total body water, arterial and venous oxygen concentration, oxygen consumption, cardiac output plus blood pyruvate and lactate levels, they were able to calculate the "excess lactate" production, which is defined as the amount of lactate produced above that secondary to non-hypoxic causes and which serves as an estimate of the energy derived from the anaerobic lactate dehydrogenase system. In these studies the anaerobic metabolic rate is defined as the slope of the "excess lactate" accumulation curve, and in normal subjects this is found to supply approximately 5 per cent of the total energy required during mild exercise. Although control subjects were thus able to supply 95 per cent of their oxygen requirements by cardio-respiratory responses through the oxygen transport system, in patients with heart failure only 50 to 80 per cent of the required energy was derived from this source and the remaining 20 to 50 per cent was supplied by the anaerobic mechanism. The values determined were found to be independent of severity and duration of effort as well as of the absolute level of circulatory and respiratory responses. The degree of anaerobic contribution to total metabolism in normal subjects did not approach that in the heart failure group as the exercise became more severe. The authors believe that although the usual role of the 5 per cent contribution to total metabolism from the anaerobic mechanism remains to be determined, the significantly increased values found in heart failure signify that these patients may deliver energy to their tissues via a different mechanism. The anaerobic pathway appears to join increased blood flow and increased oxygen extraction as a method by which patients with congestive failure meet their energy demand. It is to be noted, however, that the latter 2 mechanisms do not have to be maximal for the former to play a significant role. The data suggest that the rate of supply of oxygen at the sites of metabolism is inadequate to meet demands in patients with congestive failure although this inadequacy may not be measured merely by the observed changes in either oxygen delivery or cardiac output.

FREEDBERG

Irisawa, A., and Rushmer, R. F.: Relationship between Lymphatic and Venous Pressure in Leg of Dog. Am. J. Physiol. **196**: 495 (Mar.), 1959.

Technics are described for the measurement of lymphatic pressure in the resting limb of the dog. In resting anesthetized dogs the lymphatic pressure has a value close to, but a little below, peripheral venous pressure. Changes in peripheral lymphatic and venous pressures are neither simultaneous nor equal. Even large changes of pressure in one system were not reflected in the other. A definite rise in lymphatic pressure was observed during spontaneous muscle movements. Fluctuation in lymphatic pressure was recorded during normal and forced abdominal respirations.

KAYDEN

Kremer, R., Brasseur, L., Mandart, M., and Lavenne, F.: Hemodynamics in So-Called Isometric Contractions of the Atrium. Acta. cardiol. **14**: 121, 1959.

The authors analyze pressure curves obtained in the brachial artery and in the heart cavities on the right during 5 instances of complete heart block, 3 instances of wandering pacemaker and on occasions of paroxysmal supraventricular tachycardia. Quasi-isometric atrial systole, corresponding to atrial systole synchronous with ventricular systole caused a sharp rise in pressure in the atrial cavities. The authors believe that atrio-

entricular regurgitation may play a part in this se in pressure. In the first patient with wandering pacemaker, provoked during catheterization of tight mitral stenosis, a difference was seen in ie behavior of the 2 ventricles. During short eriods of slow nodal rhythm, right ventricular ystolic pressure clearly decreased, while the brahial artery pressure remained unchanged. The uthors attributed this ventricular discrepancy to he important difference in ventricular filling conitions seen on each side of the heart in mitral tenosis and to the anatomic constitution of pure nitral stenosis, which makes impossible any reurgitation through the mitral valve. In another atient with wandering pacemaker, and pulmonary eart disease, the arterial pressures in the lungs nd peripherally, showed an important decrease luring periods of nodal rhythm.

BRACHFELD

Lim, T. P. K., and Luft, U. C.: Alterations in Lung Compliance and Functional Residual Capacity with Posture. J. Appl. Physiol. **14**: 164 (Mar.), 1959.

The relationship between lung compliance and the resting end-expiratory volume was determined in the same individuals where physiological changes in the size of functional residual capacity were induced by varying body positions relative to gravity. Six normal subjects were investigated in the erect standing and the supine lying positions. Both lung compliance and functional residual capacity were proportionally reduced when the supine position was taken after standing. Specific compliance, therefore, remained the same at the 2 body positions.

RINZLER

Linderholm, H., and Strandell, T.: Heart Volume in the Prone and Erect Positions in Certain Heart Cases. Acta med. Scandinav. **162**: 247, 1958.

Sixty-seven patients with heart disease and 42 control subjects were studied roentgenologically to determine the heart volume in the prone and erect positions, and in all groups the mean heart volume was higher in the prone than in the erect posture. When the difference between the prone volume (V_p) and the erect volume (V_ϵ) and the ratio of these 2 values (V_p/V_ϵ) were calculated, (V_p/V_ϵ) and V_p-V_ϵ were found to be smallest in those patients with pulmonary stenosis, mitral stenosis and vasoregulatory asthenia. The mean values for V_p-V_ϵ and V_p/V_ϵ were found to differ significantly when the mitral stenosis group was compared to all other groups. After valvotomy in patients with mitral stenosis the V_p/V_ϵ ratio increased as did V_p-V_ϵ, although the mean heart volume in all 9 patients so studied decreased. No relationship was found between V_p/V_ϵ and V_p-V_ϵ and the sex of patients with mitral stenosis, the pulse rate change in a 7 minute orthostatic test, the ratio of height to total hemoglobin content and the absolute heart volume. The authors postulate that the small difference seen between V_p and V_ϵ in patients with mitral stenosis may be explained by the fact that the patients have smaller orthostatic redistribution of blood volume since the change in blood volume of the left atrium and the lungs is limited by the elevated pressure in the lesser circulation. In this study also, the authors compared 2 roentgenologic technics for determining the heart volume in the prone position. Both the Larsson-Kiellberg method and Jonsell's method agreed fairly well except in patients with small sagittal diameter in whom the former method which places more weight on the 3 measured heart diameters seemed to give more accurate values.

FREEDBERG

Regan, T., Christensen, R. C., Wada, T., Talmers, F. N. and Hellems, H. K.: Myocardial Response to Acetyl Strophanthidin in Congestive Heart Failure: A Study of Electrolytes and Carbohydrate Substrates. J. Clin. Invest. **38**: 306 (Feb.), 1959.

By obtaining simultaneous samples from the coronary sinus, right atrium and brachial artery, the authors were able to determine the arterial and venous levels of oxygen, carbon dioxide, glucose, pyruvate, lactate, sodium, potassium and calcium following the injection of 1.1 mg. of acetyl strophanthidin into the right atrium and were able to study myocardial ion transfer and carbohydrate metabolism during recovery from cardiac failure. Since earlier studies indicated that increased coronary blood flow had no significant influence upon coronary arteriovenous differences of potassium concentration, it was felt that observed changes during acetyl strophanthidin administration could be attributed to the net movement of ions per se. The study group was composed of 18 patients with heart failure. Hemodynamically, the digitalis preparation led to an increase in cardiac output, stroke output, stroke work between 5 and 15 minutes following infusion in the majority of cases. No significant change was noted in myocardial oxygen extraction, carbon dioxide production, myocardial water transfer, pyruvate or glucose extraction although lactate arteriovenous differ-

ence showed a substantial decrease 15 minutes limited physical examination. The V_{3R} lead was fairly sensitive in the detection of right ventricular after the acetyl-strophanthidin was given. In 17 of the 18 patients studied a rapid movement of potassium from the heart was found, usually occurring 4 minutes after infusion. The decrement of cellular potassium from the heart was calculated to be between 3 and 7 per cent, but there was no correlation between potassium loss and hemodynamic response to the drug. No significant changes were noted in sodium or calcium levels during the period following infusion. The authors believe that this experimental design caused a temporal telescoping of events which normally occur during slower digitalization. The values for arterial and venous potassium revealed a persistently negative phase of net potassium balance even following the period of peak therapeutic response. No direct evidence was presented as to either the mechanism or effect of this change.

FREEDBERG

Rodbard, S., Williams, F., and Williams, C.: The Spherical Dynamics of the Heart (Myocardial Tension, Oxygen Consumption, Coronary Blood Flow and Efficiency. Am. Heart J. 57: 349 (Mar.), 1959.

Studies are reported utilizing a method permitting the continuous direct measurement of the cardiac output and coronary arteriovenous oxygen differences, and blood pressure and heart rate, in innervated metabolically normal dogs. The results were analyzed from the point of view that the heart behaves like a contracting sphere. On this basis, it was found that pressure work of the heart was equivalent to the volume work and that oxygen consumption was dependent on intramyocardial tension. The latter was calculated as half the product of the intracardiac radius and pressure. Recalculation of cardiac performance with this approach in a number of reports in the literature indicated that this relatively simple relationship could resolve previously contradictory data. The basis for this type of analysis and a number of physiologic and clinical aspects of cardiac function are discussed.

SAGALL

Ruosteenoja, R., Linko, E., Lind, J., and Sellberger, A.: Heart Volume Changes at Rest and During Exercise. Acta med. scandinav. 162: 263, 1958.

In order to evaluate the magnitude of change in heart volume occurring during a single heart beat and the change in this parameter occurring during exercise, the authors studied 18 healthy young sportsmen by means of serial bi-plane chest x-rays. Six sets of films per second were taken at rest and approximately 5, 12, and 17 minutes after the beginning of exercise on a bicycle ergometer. The theoretical heart volume was calculated on the basis of the length (LD), breadth (BD), and depth diameters (DD). During the cardiac cycle the heart volume was found to change approximately 40 ml. (5.4 per cent of mean volume), while during exercise the change was 55 ml. (8.7 per cent of mean volume). The BD varied mostly, the LD less, while the DD was not significantly changed. The mean heart volume during each beat fell during exercise and the great decrease was seen in the LD. The heart volume was about 99 ml. (13 per cent) smaller when a steady state was reached after 10 to 15 minutes of exercise. No significant differences were noted with regard to the degree of training of the subjects. Although the authors postulate that this may be due to the fact that only moderate work loads were used.

FREEDBERG

Schlant, R. C., Novack, P., Kraus, W. L., Moore, C. B., Haynes, F. W., and Dexter, L.: Determinations of Central Blood Volume. Comparison of Stewart-Hamilton Method with Direct Measurements in Dogs. Am. J. Physiol. 196: 499 (Mar.), 1959.

Central blood volume (cardiac output times mean transit time) from right atrium to ascending aorta was determined by the indicator-dilution method in 22 open-chest dogs. The red blood cells had previously been tagged with Cr^{51}. The actual amount of blood in the heart and lungs was calculated from the total radioactivity in the blended homogenate of these organs. The 2 measurements of central blood volume correlated well, the indicator-dilution volumes being 12 per cent greater. The discrepancy in measurements was probably related to the lower hematocrit level in the pulmonary circuit than in the larger vessels.

KAYDEN

UNCOMMON FORMS OF HEART DISEASE

Handforth, C. P., and Woodbury, J. F. L.: Cardiovascular Manifestations of Rheumatoid Arthritis. Canad. M. A. J. 80: 86 (Jan. 15), 1959.

The clinical courses and autopsy findings were summarized for 3 patients who had chronic rheumatoid arthritis of the limbs, plus associated fatal cardiac disease. One patient, a 16-year-old girl, developed a sterile fibrinopurulent

pericarditis with effusion and tamponade during an advanced state of deterioration from rheumatoid arthritis. Another, a 68-year-old woman with moderate rheumatoid disease, died soon after developing syncope with complete heart block. At autopsy the sole cardiac abnormality was a sizable granuloma involving the upper end of the interventricular septum. The third patient, a 66-year-old man with moderate long-term rheumatoid disease, died from subacute congestive heart failure: autopsy showed widespread inflammation of the smaller arteries of the heart, pancreas, and skeletal muscle which appeared to be of rheumatoid origin.

ROGERS

VALVULAR HEART DISEASE

Joly, F., Azerad, J., Azerad, N, and Carlotti, J.: Correlation of Electrocardiographic and Hemodynamic Postoperative Data in 80 Cases of Tight Mitral Stenosis. Acta Cardiol. **13:** 587, 1958.

Eighty patients, aged 15 to 42, who underwent a commissurotomy for tight mitral stenosis 8 to 24 months before this study are reported. Regression of P-wave abnormalities occurred early in the first few weeks postoperatively, but these changes were of unequal reliability. Only the height of the P wave and its morphologic pattern correlated with the hemodynamic data, whereas its axis and duration did not. The electrocardiographic signs of right ventricular strain decreased more slowly over a period of months and even years. This was observed in each case in which mitral and arteriolar resistance fell. This regression was complete in 33 patients, incomplete in 13, and absent only in the 3 in which the commissurotomy failed. However, only in half the patients did such a complete regression of electrocardiographic abnormalities correspond to a normalization of hemodynamic data.

BRACHFELD

Salerno, R. A.: The Experimental Production of Valvular Aortic Stenosis. Ann. Surg. **149:** 368 (Mar.), 1959.

Stenosis of the aortic valve was produced by clipping the aortic commissures with clips of stainless steel wire .030 inches in diameter and measuring 5 to 10 mm. in length. The dogs were given 0.5 mg. of Digoxin intramuscularly at 8-hour intervals on the day before operation and the clips were applied to 2 or 3 aortic commissures through a vertical incision in the ascending aorta exposed through a right thoracotomy incision. The dogs were under sodium pentothal anesthesia with venous inflow occluded for 45 seconds. In 16 dogs, all 3 commissures were clipped during general hypothermia. Eight died at operation and 2 additional ones in the first 24 hours. Ventricular fibrillation occurred in 10 animals and was irreversible in 2. Aortic insufficiency developed in 4 dogs of this group in each instance due to a defect in the construction of a clip. Left heart catheterization was performed in 5 of the 6 chronic survivors. Systolic pressure gradients across the aortic valve ranged from 30 to 70 mm. Hg. All the surviving animals had systolic murmurs and thrills over the aortic area. In 17 dogs, 2 of the 3 commissures were clipped under general hypothermia. Five animals died at operation, 4 within 24 hours and 2 within 48 hours. Ventricular fibrillation occurred in 6 animals and was reversible in all but 1. Systolic gradients in 3 catheterized chronic survivors in this group were 12, 15 and 52 mg. Hg. In a final series of 15 animals, again 2 commissures were clipped with the animals normothermic. Of these, only 2 died during operation and 2 others during the first 48 hours. Ventricular fibrillation occurred in only 2 animals and was reversible in both instances. Four animals died, at intervals of 4 to 8 days after operation, of left ventricular failure. Eight dogs were chronic survivors and in these left heart catheterization demonstrated aortic systolic pressure gradients of 20 to 80 mm. Hg. Postmortem studies revealed early a deposition of red, filmy fibrous exudate over the clips and the fixed commissures. Fibrosis was apparent within 7 days. By 1 month, most of the clips and commissures were imbedded in dense scar. The mobility of the leaflets was impaired and the aortic orifice in most cases was reduced to 5 mm. or less. The unclipped commissure was always free of pathologic change. Calcium deposition was found on the fused commissures of 2 of the 4 animals sacrificed at 3 months. Ventricular dilatation but not muscular hypertrophy was observed in this period of study. Hypothermia increased ventricular irritability and reduced survival. It is believed that this preparation simulated aortic stenosis as it occurs in man.

LEVINSON

Schnabel, T. G., Jr., Eliasch, H., Thomasson, B., and Werko, L.: The Effect of Experimentally Induced Hypervolemia on Cardiac Function in Normal Subjects and Patients with Mitral Stenosis. J. Clin. Invest. **38:** 117 (Jan.), 1959.

Hypervolemia was induced by intravenous infusions of a variety of solutions in 31 normal

subjects and in 15 patients with mitral stenosis. Infusion of distilled water, saline, and 3 per cent glucose in water, in normal subjects, produced no significant changes in cardiovascular dynamics except for an increase in blood volume of 5 to 8 per cent. Infusions of dextran solutions were associated with increases of blood volume of 20 to 35 per cent in normal patients and 10 to 29 per cent in patients with mitral stenosis. Extensive data are presented on the effects of these infusions on cardiac and stroke outputs, on renal hemodynamics, and on right ventricular stroke work. The authors state that their data refute the assumption that the filling pressure is the main determinant of the level of cardiac output or cardiac work.

KARPMAN

VASCULAR DISEASE

Collins, J. H., Bosco, J. A. S., and Cohen, C. J.: Pregnancy Subsequent to Ligation of the Inferior Vena Cava and Ovarian Vessels. Am. J. Obst. & Gynec. **77**: 760 (April), 1959.

There were 47 instances of pregnancy subsequent to ligation of the inferior vena cava and ovarian vessels in 140 women. The ligation was carried out because of severe suppurative pelvic thrombophlebitis that was not responding to other measures, or for pulmonary infarction. Thirty of the pregnancies extended beyond 28 weeks, and 22 progressed to term. The antenatal, intrapartal, or puerperal course was not influenced by the interruption of normal venous return. The ligation of the inferior vena cava and ovarian veins does not contraindicate pregnancy. Special care is not necessary in managing the patient who subsequently conceives.

SHEPS

Cranley, J. J., Krause, R. J., and Strasser, E. S.: Limb Survival with and without Definitive Surgical Treatment in Obliterative Arterial Disease. Surgery **45**: 32 (Jan.), 1959.

A series of patients with obliterative peripheral arterial disease was studied following conservative therapy, lumbar sympathectomy, thromboendarterectomy, or arterial graft. The survival rate in 5 clinical stages of the disease was used as a criterion of estimating the therapeutic results. In grades I and II patients (a decrease or absence of the dorsalis pedis and posterior tibial pulses) conservative therapy gave good results and would appear indicated until a major arterial occlusion appears. A lumbar sympathectomy when done in this group was performed as the second side of a bilateral operation in which the prime indication was more advanced disease in the opposite extremity. In grade III patients (absence of the popliteal pulse) lumbar sympathectomy was recommended for the good-operative-risk patients under 70, but was rarely urged. In some thrombarterectomy and arterial graft were indicated. Surgical therapy was recommended for group IV (rest pain or rubor of the foot on dependency) and group V patients (continuous pain, petechial hemorrhages of the dorsum of the foot, or skin necrosis) unless there were strong medical contraindications. With group IV and V patients the amputation rate rose sharply. The most important determinant of the result of treatment proved to be the severity of the ischemic process when the patient first consulted the physician.

SAGALL

Erskine, J. M., and Gerbode, F.: The Surgical Treatment of Aneurysms of the Abdominal Aorta with Resection and Grafting. A Study of the Hazards, Mortality and Results. Am. J. Surg. **97**:270 (Mar.), 1959.

Thirty patients with abdominal aortic aneurysms underwent surgery. The overall mortality was 20 per cent. The present operative mortality rate is about 5 per cent for the elective resection of an unruptured abdominal aneurysm. Ruptures had already occurred in 5 patients at the time of the surgery and of 2 patients in whom shock was present, 1 died. Of the remaining 3 patients there was 1 death which could not be attributed to the loss of blood. There were a total of 6 deaths. Shock and renal failure were seen in 3 patients each. Twenty-seven of the patients had renal disease demonstrated pre-operatively and half of these had post-operative renal complications. On the other hand, renal complications after surgery developed in only 3 per cent of patients in whom no renal disease was demonstrated pre-operatively. Twenty-two patients had mild to severe peripheral vascular disease present pre-operatively. In 4 the femoral area was explored subsequently, and in 3, additional grafts were used. There were 2 patients with post-operative gangrene of the leg. This problem contributed to the death of 4 patients. Seventeen patients had cardiac abnormalities pre-operatively and there were no serious complications related to this finding. Hemorrhage with shock and renal failure occurred in 2 patients as a result of bleeding from 1 of the small lumbar vessels of the homograft. There were 3 instances of early thrombosis in and distal to

the graft. One occurred in a teflon graft and the remaining 2 in homografts. All were attributable to difficulties associated with an inadequate outflow tract. Sepsis contributed to death in 2 patients and intestinal obstruction in 1 patient. Of the 24 survivors, 23 have been evaluated and 1 was lost to follow-up. The only late complication related to surgery was 1 case of homologous serum jaundice. No thrombosis or aneurysmal dilatation had occurred. Intermittent claudication was partially or completely relieved in most patients. However, 3 patients noted a progression of their claudication and 1 of these had a hypogastric artery ligated at the time of the operation because of extensive arteriosclerosis. One patient died of heart disease 2 years following surgery and in 1 other patient there was evidence of progression of the heart disease. In an addendum to the paper it was noted that 12 additional patients were operated on successfully, making the overall mortality 14 per cent for the entire series.

SHEPS

Morris, G. C., Jr., DeBakey, M. E., Cooley, D. A., and Crawford, E. S.: Arterial Bypass Below the Knee. Surg., Gynec. & Obst. **108:** 321 (Mar.), 1959.

Occlusive arteriosclerotic disease of the lower extremities is usually segmental and involves mainly the superficial femoral arteries. The preferred treatment is bypass grafting which, in the authors' experience with 317 patients, has been followed by pulsatile blood flow in the lower leg in 86 per cent. In most instances the distal graft site is the supragenual portion of the popliteal artery, but occasionally the infragenual portion must be used. The present report describes the technical aspects of using the latter site emphasizing the ease of approach through a medial incision below the knee, the paucity of collateral vessels which are sacrificed and the tunneling of a crimped Dacron prosthesis through Hunter's canal from the proximal graft site. Thirty-three patients have received this type of graft and 8 of these case histories plus pre- and postoperative arteriograms are presented. Late thrombosis of the graft occurred in 10 patients of whom 6 underwent re-operation. Examinations as long as 18 months postoperatively have indicated that in 76 per cent of these 33 patients the grafts continued to function. The patients were advised not to flex the knee beyond 90° which represents no significant handicap to this relatively elderly group.

ROGERS

Scott, H. W., Jr., Foster, J. H., Kirtley, J. A., and Carlson, R. I.: Follow-up Study of Patients with Arteriosclerotic Aneurysm of the Abdominal Aorta Treated by Resection and Freeze-Dried Homograft. Surgery **45:** 445 (Mar.), 1959.

Forty patients with arteriosclerotic aneurysm of the abdominal aorta who were treated by aneurysmectomy and interpolation of a freeze-dried homograft were followed for 1 to 4 years postoperatively. An excellent immediate result was obtained by 26 patients. Six other patients obtained a good result but were restricted by other disease processes. There were 8 deaths in hospital. Four of these deaths occurred among 8 patients who had a ruptured aneurysm. In the nonruptured group the mortality rate was 12.5 per cent. The mortality dropped as the experience grew. Renal shutdown occurred in 4 patients, 2 of whom survived. Three patients died from severe infections. One patient died of myocardial infarction and another of dissecting thoracic aneurysm with rupture. In addition 1 patient developed gangrene of the leg, which required amputation, and 2 developed thrombophlebitis. Excluding the cases of renal shutdown, a rise in serum nonprotein nitrogen in excess of 45 mg. per cent was sustained by 25 of the patients. This is said to reflect a renal-vaso-constrictive response to temporary aortic occlusion. The use of sympathetic blocking agents, e.g. Arfonad, has proved helpful during aortic occlusion. Its use in 5 patients was accompanied by a normal postoperative serum nonprotein nitrogen level and excellent urinary output. All patients have been followed. There have been 5 late deaths that were unrelated to the abdominal aneurysm or its treatment. These occurred 3 to 20 months postoperatively. Pathologic examination of the grafted aorta in 4 of these patients revealed a patent functioning graft with no evidence of aneurysmal change, thrombosis, infection, or stenosis. One further patient had been partially disabled by a cerebrovascular accident that occurred 6 months following operation. Twenty-six survivors had led a full and active life. There was no further evidence of aneurysm formation or impairment of circulation to the lower extremities. The 2- and 3-year survival rates are each 67 per cent, and the 4-year survival figure, 69 per cent. The overall survival was 68 per cent. The survivorship of patients with abdominal aortic aneurysms was greatly increased by aneurysmectomy and replacement with graft. The freeze-dried homograft was shown by this study to be an excellent

aortic substitute over the period of observation of 1 to 4 years.

SHEPS

Singleton, A. O., Jr., McGinnis, La M. S., and Eason, H. R.: Arteritis Following Correction of Coarctation of the Aorta. Surgery 45: 665 (April), 1959.

Two cases are presented of necrotizing arteritis occurring in the small vessels distal to a corrected coarctation of the aorta. Five reported cases are also reviewed. In 6 patients the symptoms were confined to the gastrointestinal tract and consisted of infarction. The onset of symptoms usually occurred in the first postoperative week. In the remaining patients, symptoms arose 3 months following operation. This patient is of particular interest because the spinal cord as well as the gastrointestinal tract was involved. Many vessels below the point of coarctation have shown histologic evidence of involvement, but the area of actual occlusion is in the terminal portions of the vessels. The pathogenesis of arterial necrosis is related to the changes in hemodynamics following operation. The abdominal vessels are subjected to an elevated systolic pressure and consequently a larger, sharply increased pulse pressure. There were 4 deaths among the 7 patients. There were no secondary attacks of arteritis that could be detected clinically in the reported cases.

SHEPS

Trumbull, W. E., Uriu, M., and Averbook, B. D.: Surgical Therapy of Acute Upper Extremity Arterial Occlusion. Ann. Surg. 149:388 (Mar.), 1959.

It has been claimed, particularly for the upper extremity, that conservative treatment of acute arterial occlusion with anticoagulants, antispasmodics and sympathetic blocks is superior to surgery. The authors have re-evaluated this view. They present 8 patients with acute arterial embolism to the upper extremity treated by the conservative medical method. All of these patients had only weak or absent radial pulses after sympathetic block and in 1 patient an amputation was necessary for gangrene. One patient died of a myocardial infarction 24 hours after the onset of arterial occlusion in the upper extremity. In 9 patients treated with embolectomy, the results were immediate in 6 with prompt return of color, warmth and radial pulse. In 1 the pulse and color returned in 30 minutes and in the other 2 there were good responses in 24 and 48 hours. The 6 patients were all operated on within 12 hours after the onset of the occlusion. There was 1 death due to pulmonary embolus 5 days after embolectomy. The authors feel that surgical extraction of the thrombus or embolus is the procedure of choice for several reasons. The operation can be done under local anesthesia; there is more rapid return of pulse, warmth and color; there have been no instances of post-operative gangrene. The use of anticoagulants, postoperatively, lessens the reformation of the thrombus at the site of the arteriotomy and the possibility of peripheral thrombi in vasospastic vessels. In 1 instance endarterectomy was performed because of atherosclerotic occlusion of the vessel. During surgery blood for transfusion should be available because of the sudden hypotension which occurs secondary to arteriotomy. The authors believe that with surgery and operative and postoperative anticoagulant therapy, good results can still be obtained up to 48 hours after the acute onset, as demonstrated in this series.

LEVINSON

Turner, M.D., Neely, W. A., and Barnett, W. O.: The Effects of Temporary Arterial, Venous, and Arteriovenous Occlusion upon Intestinal Blood Flow. Surg., Gynec. & Obst. 108:347 (Mar.), 1959.

In anesthetized dogs the blood flow in an ileal segment was estimated by recording changes in its weight. The flow was more markedly reduced following a 30-minute occlusion of the venous supply than after 1 hour of arterial occlusion, possibly because the bowel became more edematous during venous stasis. Only slight flow reduction followed 1 hour of arterial plus venous stasis. Occlusion of the segmental artery for 4 hours in 6 dogs resulted in the death of 2, of which 1 had gangrene. Similar occlusion of the vein in 6 dogs resulted in gangrene in 4 and death in 4.

ROGERS

Williams, R. D., and Carey, L. C.: Studies in the Production of "Standard" Venous Thrombosis. Ann. Surg. 149:381 (Mar.), 1959.

Thrombi were produced with regularity in the external jugular veins of dogs. These were produced by the passage of an electric current through electrodes incorporated within a leucite cuff placed about the exposed vein. A fairly uniform clot could be produced in 100 per cent of the animals with a current of 5 milliamperes acting over an hour; nembutal anesthesia was used. With the use of heparin in an amount sufficient to prolong the coagulation time to

twice the preheparin value the clot was prevented in 100 per cent of the animals. With Dicumarol and prothrombin levels of 3 to 15 per cent only 4 of 12 animals failed to develop clots. When the prothrombin time fell to well below 3 per cent, thrombosis did fail to occur but marked bleeding was noted on exposing the veins of dogs with prothrombin values of less than 5 per cent. It appeared in these experiments that local tissue damage occurring at the positive electrode was the main factor in the production of the thrombus. It is felt that heparin may prevent the action of thrombin on fibrinogen, but that with the available thromboplastin from severe tissue damage even the small amounts of prothrombin which can be converted to thrombin will be present even after a therapeutic dose of Dicumarol. The mechanism of clot formation, of course, requires further elucidation.

LEVINSON

Winblad, J. N., Reemtsma, K., Vernhet, J. L., Laville, L. P., and Creech, O.: Etiologic Mechanisms in the Development of Collateral Circulation. Surgery **45**: 105 (Jan.), 1959.

Observations concerning the relative roles of pressure and anoxia in the development of collateral circulation in dog experiments and in clinical cases of occlusive peripheral vascular disease are reported. In the dog following acute occlusion of the superficial femoral artery the development of collateral circulation, as measured by arteriography and distal pressure tracings, appeared to correspond directly with the pressure gradient at the site of occlusion. Anoxia of the tissues distal to the site of occlusion did not appear to play any significant role, since perfusion of the extremity distal to occlusion with saturated and unsaturated blood produced no appreciable effect on the development of collateral circulation. In 31 patients clinical studies were performed with arteriograms and intra-arterial pressure tracings taken before and after operation at selected sites above and below areas of occlusion. The clinical studies confirmed the experimental observations that pressure gradients are a determinant of collateral flow. In the clinical cases the intraarterial pressure tracings obtained distal to an obstructed segment frequently proved superior to arteriography as a reflection of collateral circulation and in the assessment of the areas of runoff.

SAGALL

REVIEWS IN CARDIOVASCULAR DISEASE

Gross, R. E., Shattuck Lecture: Open-Heart Surgery for Repair of Congenital Defects. New England J. Med. **260**: 1047 (May 21), 1959.

Hook, O., and Norlen, G.: Aneurysms of the Middle Cerebral Artery. Acta Chir. scandinav., Supp. 235, 1958.

Hultgren, H., and Leo, T.: Phonocardiographic Features of Combined Mitral Stenosis and Insufficiency. Medicine **38**: 103 (May), 1959.

Leo, T., and Hultgren, H.: Phonocardiographic Characteristics of Tight Mitral Stenosis. Medicine **38**: 85 (May), 1959.

Southwood, A. R.: Aspects of Preventive Cardiology. Lancet **1**: 435 (Feb. 28), 1959.

NEWS FROM
THE AMERICAN HEART ASSOCIATION

44 East 23rd Street, New York 10, N.Y.
Telephone Gramercy 7-9170

Renew Journal Subscriptions Through Heart Association

Renewals of subscriptions for 1960 of *Circulation* and *Circulation Research*, official journals published by the Association, should be made through the Publishing Director, American Heart Association, 44 East 23rd Street, New York 10, N.Y. Annual subscription rates are: *Circulation* (12 issues) $14 in the U.S. and Canada, $15 elsewhere. *Circulation Research* (6 issues) $9 in the U.S. and Canada, $10 elsewhere. (Special annual rate for full-time research fellows, $7.) Combined subscription to both Journals, $21 in the U.S. and Canada, $23 elsewhere.

Revised RF Statement Available; Congenital Defects Booklet Issued

The revised statement on "Prevention of Rheumatic Fever and Bacterial Endocarditis Through Control of Streptococcal Infections" which appeared in the January, 1960, issue of *Circulation* has been reprinted in leaflet form by the Association.

The Association has also published a new booklet, "If Your Child Has a Congenital Heart Defect." Intended to reinforce the physician's advice to parents relating to diagnosis, surgery and postoperative care, it is addressed primarily to parents of patients whose defects are operable.

Copies of the leaflet and booklet are obtainable through local Heart Associations or the American Heart Association.

Community Services Expansion Studied Through New AHA Fund

Grants totaling approximately $34,000 to help support programs in the field of community service and education have been allocated on a one-year trial basis to six affiliates by the American Heart Association. The grants were made from a new community service and development fund. Supplementary funds will be provided by local Associations conducting the pilot programs.

Projects receiving support under the new grants include:

A study of school health education activities in Los Angeles County; establishment of a "traveling" Work Evaluation Unit in Virginia, as part of a statewide rehabilitation program; expansion of a North Carolina program seeking methods through which persons in small communities can receive the benefit of recent advances in cardiovascular medicine; a pilot study in Baltimore to determine the possible benefits of home care as compared to hospital care for a group of cardiac patients; a mass blood-typing program in Pittsburgh to simplify blood procurement needs in open heart surgery; a study in Washington state to explore and describe factors important in successful patient participation in rheumatic fever prophylactic programs.

Awards of Merit, Other Honors Bestowed on Physicians by AHA

Six Awards of Merit for distinguished service in the development of the Association's national program of research, education and community services were presented at the meeting of the Board of Directors in December. Also cited for outstanding services were 15 past members of the national Research Committee.

Recipients of the Award of Merit were: Drs. J. Scott Butterworth, New York; George C. Griffith, Los Angeles; Kenneth G. Kohlstaedt, Indianapolis; Louis E. Viko, Salt Lake City;

ouis I. Dublin, Ph.D., New York; and Mr. eorge E. Merrifield, Cleveland.

Members of the Research Committee who ere cited for serving full five-year terms or Chairmen of the committee were: Drs. obert H. Bayley, Oklahoma City; Howard . Burchell, Rochester, Minn.; Charles A. R. onnor, New York; Arthur C. Corcoran, leveland; Jefferson M. Crismon, Stanford, al.; Harold D. Green, Winston-Salem, N.C.; ohn C. Jones, Los Angeles; Louis N. Katz, hicago; Ancel Keys, Ph.D., Minneapolis; nn G. Kuttner, New York; Howard B. prague, Boston; Eugene A. Stead, Jr., Durham, N.C.; Lewis Thomas, New York; Francis '. Wood, Philadelphia; and Harland G. Wood, Ph.D., Cleveland.

Association's Work Evaluation Units Schedule National Conference

A national conference of Work Evaluation Units to review the latest techniques for safely returning cardiacs to employment is scheduled to be held at Arden House, Harriman, N.Y., on May 2-4, 1960. Physicians, social workers, psychiatrists, psychologists and rehabilitation counselors from the more than 50 Work Evaluation Units sponsored by Heart Association affiliates and chapters are expected to attend. Other participants will include representatives of the U.S. Office of Vocational Rehabilitation, Public Health Service, Employment Service, and employers, labor and other interested groups.

Full Issue of Heart Bulletin Devoted to Congestive Failure

As part of the Heart Association's professional education program on congestive heart failure, the entire January-February issue of *The Heart Bulletin* is devoted to this subject. Contents and authors are:

"The Lung in Congestive Heart Failure," Noble O. Fowler, M.D.; "Heart Failure in Pregnancy," James Metcalfe, M.D.; "The Heart and Heart Failure," James V. Warren, M.D.; "Heart Failure in the Pediatric," Edward C. Lambert, M.D.; "Long Term Management," R. Bruce Logue, M.D.; "Emergency Treatment in Congestive Heart," George E. Burch, M.D.; "The Kidney in Congestive Heart Failure," Louis Leiter, M.D. and Jacob Grossman, M.D.; and "Rehabilitation: New Success in Old Failure," John O. Smith, M.D.

The Heart Bulletin is sponsored by the AHA in cooperation with the National Heart Institute and the American Academy of General Practice, and published by The Medical Arts Publishing Foundation, Houston, Tex.

New Attendance Record Set at AHA Scientific Sessions

A new attendance record of more than 5,000 physicians, scientists, nurses and lay leaders was set at the 1959 Annual Meeting and Scientific Sessions of the American Heart Association in Philadelphia, October 23-27. In 1958 the comparable figure was 3,375.

Name New Publishing Director

Robert Okin has been named Publishing Director of *Circulation* and *Circulation Research* to succeed Alan Baird Hastings who resigned to accept a position as Director of Publications and Public Relations at McLean Hospital, Belmont, Mass. Mr. Okin was formerly Research and Program Reporter for the Association's Public Information Department.

New Heart Journal in Japan

"Japanese Heart Journal," a new quarterly in English devoted to outstanding cardiovascular studies conducted in Japan, began publication in January, 1960, under the auspices of the University of Tokyo Faculty of Medicine. Copies are available free of charge if requested promptly from Hideo Ueda, M.D., Chief Editor, 1 Motofuji-cho, Bunkyo-Ku, Tokyo.

Symposium Held in Poland On Spatial Vectorcardiography

Proceedings of the Symposium on "Theory, Technique and Clinical Application of Spatial Vectorcardiography," held in Wroclaw, Poland, October 21-24, will be available in 1961. Prof. Hugon Kowarzyk chaired the meetings at which papers were presented from nine European countries, the United States and

Mexico. Proceedings will be obtainable from the Wroclaw Medical Academy of Science, 1 Marcinkowskiego, which sponsored the symposium.

Inter-American Cardiology Congress

Registration forms for the Sixth Inter-American Congress of Cardiology in Rio de Janeiro, August 14-20, 1960, are now available. They may be obtained from Dr. Hugo Alqueres, Secretary, P.O. Box 1594, Rio de Janeiro, Brazil.

Meetings Calendar

March 17-19: International Symposium on "The Blood Platelets," Detroit (*by Invitation Only*). Shirley A. Johnson, Henry Ford Hospital, Detroit 2, Mich.

March 19-24: American Academy of General Practice, Philadelphia. Mac F. Cahal, Volker Blvd. at Brookside, Kansas City 12, Mo.

March 21-24: Southeastern Surgical Congress, New Orleans. B. T. Beasley, 1032 Hurt Bldg., Atlanta 3, Ga.

March 26-27: American Psychosomatic Society, Montreal. Eric Wittkower, 265 Nassau Road, Roosevelt, N. Y.

March 28-31: Southwestern Surgical Congress, Las Vegas. Mary O'Leary, 1213 Medical Arts Building, Oklahoma City, Okla.

April 1-3: American Society of Internal Medicine, San Francisco. R. L. Richards, 350 Post Street, San Francisco 8, Calif.

April 3-6: American Surgical Association, White Sulphur Springs, W. Va. W. A. Altemeier, Cincinnati General Hospital, Cincinnati 29, Ohio.

April 4-9: American College of Physicians, San Francisco. E. R. Loveland, 4200 Pine Street, Philadelphia 4, Pa.

April 11-15: American Physiological Society, Chicago. Ray G. Daggs, 9650 Wisconsin Ave., Washington 14, D. C.

April 11-16: American Association of Anatomists, New York. Louis B. Flexner, University of Pennsylvania Medical School, Philadelphia 4, Pa.

May 1-2: American Society for Clinical Investigation, Atlantic City. S. J. Farber, 550 First Ave., New York 16, N. Y.

May 3-4: Association of American Physicians, Atlantic City. P. B. Beeson, Yale University School of Medicine, New Haven 11, Conn.

May 11-13: American Association for Thoracic Surgery, Miami Beach. H. T. Langston, 7730 Carondelet Ave., St. Louis 5, Mo.

May 23-28: American College of Cardiology, Indianapolis. Philip Reichert, 2709 Empire State Bldg., New York 1, N. Y.

June 8-12: American College of Chest Physicians, Miami Beach. Murray Kornfeld, 112 E. Chestnut St., Chicago 11, Ill.

June 11: International Cardiovascular Society, North American Chapter, Miami Beach. P. J. DeCamp, 3503 Prytania St., New Orleans 15, La.

June 13-17: American Medical Association, Annual Meeting, Miami Beach. F. J. L. Blasingame, 535 N. Dearborn, Chicago 10, Ill.

August 8-11: National Medical Association, Pittsburgh. John T. Givens, 1108 Church Street, Norfolk, Va.

August 21-26: American Congress of Physical Medicine and Rehabilitation, Washington, D. C. Mrs. Dorothea C. Augustin, 30 N. Michigan, Chicago 2, Ill.

Abroad

May 2-11: Pan American Medical Association Congress, Mexico City. Joseph J. Eller, 745 Fifth Avenue, New York 22, N. Y.

May 6-8: International Congress of Phlebology, Chambery, France. J. Marmassee, 3 Rue de la Republique, Orleans, Loiret, France.

May 15-18: International College of Surgeons, International Congress, Rome. Secretariat, 1516 Lake Shore Drive, Chicago 10, Ill.

May 30-June 3: Asian-Pacific Congress of Cardiology, Melbourne, Australia. A. E. Doyle, Alfred Hospital, Melbourne S. 1, Victoria, Australia.

June 2-4: International Symposium on Drugs Affecting Lipid Metabolism, Milan, Italy. Prof. S. Garattini, Institute of Pharmacology, Via A. del Sarto 21, Milan, Italy.

August 14-20: Inter-American Congress of Cardiology, Rio de Janeiro. Magalhaes Gomes, Av. Nilo Pecanha, 38, Rio de Janeiro, Brazil.

August 24-27: International Congress of Internal Medicine, Basel, Switzerland. Secretariat, 13, Steinentorstre, Basel, Switzerland.

August 28-September 1: International Congress on Diseases of the Chest, Vienna. Murray Kornfeld, American College of Chest Physicians, 112 E. Chestnut, Chicago 11, Ill.

September 1-3: First International Congress of Nephrology, Geneva. G. Richet, 149 Rue de Sevres, Paris 15, France.

September 18-25: European Congress of Cardiology, Rome. Secretariat, Clinica Medica, University of Rome, Italy.

1962: Fourth World Congress of Cardiology, Mexico City. I. Chavez, Ave. Cuauhtemoc 30, Mexico, D. F.

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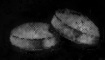

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Circulation

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